FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE (pedsODAC)

Virtual Meeting

Friday, June 16, 2023

10:00 a.m. to 2:50 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: Hi. It's 10:00. Good morning, and welcome. It's hard to believe that it's been a year since we last got together. I hope that everybody's doing ok. I'm extremely excited to be chairing this ODAC meeting, where we will be discussing dosage optimization of new drugs and biological products for pediatric patients with cancer. 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 email is currently displayed.

My name is Dr. Alberto Pappo, and I will be chairing this meeting. I will now call the June 16, 2023 Pediatric Oncology Subcommittee of the Oncologic Drug Advisory Committee meeting to order. Dr. Takyiah Stevenson is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Subcommittee

DR. STEVENSON: Good morning. My name is Takyiah Stevenson, and I'm the acting designated federal officer for this meeting. When I call your name, please unmute yourself and turn on your camera. Please introduce yourself by stating saying your name and affiliation for the record. We will first start with ODAC members.

Mr. Mitchell?

MR. MITCHELL: Good morning. I'm David Mitchell. I'm the consumer representative to the ODAC.

DR. STEVENSON: Dr. Pappo?

DR. PAPPO: Hi. My name is Alberto Pappo. I'm a pediatric oncologist, and I'm the chair of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee.

DR. PAPPO: Next, is ODAC's non-voting member, industry representative, Dr. Cheng.

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

DR. STEVENSON: We'll now go to our temporary members, and begin with Dr. Balis.

DR. BALIS: Hi. Frank Balis at the Children's Hospital in Philadelphia.

DR. CUDKOWICZ: Dr. DuBois?

DR. DuBOIS: Steve DuBois at Dana-Farber/ Boston Children's.

DR. STEVENSON: Dr. Glade Bender?

DR. GLADE BENDER: Good morning. I'm Julia Glade Bender, pediatric oncologist from Memorial Sloan Kettering.

DR. STEVENSON: Dr. Kolb?

DR. KOLB: Good morning. Andy Kolb, pediatric oncologist with The Leukemia and Lymphoma Society.

DR. STEVENSON: Dr. Laetsch?

DR. LAETSCH: Good morning. I'm Theodore Laetsch at the Children's Hospital in Philadelphia.

DR. STEVENSON: Ms. Ludwinski?

MS. LUDWINSKI: Hi. Donna Ludwinski, patient representative with Solving Kids Cancer.

DR. STEVENSON: Dr. Meany?

DR. MEANY: Good morning. I'm Holly Meany, a pediatric oncologist at Children's National Hospital in Washington, DC.

DR. STEVENSON: Dr. Mody?

DR. MODY: Yes. Hi. I'm Rajen Mody, University of Michigan, pediatric oncologist.

DR. STEVENSON: Dr. Parsons?

DR. PARSONS: Hi. I'm Will Parsons, pediatric oncologist at Texas Children's Hospital and Baylor College of Medicine.

DR. STEVENSON: Dr. Smith?

DR. SMITH: Good morning. I'm Malcolm Smith. I'm a pediatric oncologist at the National Cancer Institute and the Cancer Therapy Evaluation Program.

DR. STEVENSON: Dr. Unguru?

DR. UNGURU: Good morning. Yoram Unguru. I am a pediatric hematologist/oncologist at the Children's Hospital at Sinai in Baltimore and bioethics at the Johns Hopkins Berman Institute of Bioethics.

DR. STEVENSON: We will now go to the FDA

participants.

Dr. Pazdur?

DR. PAZDUR: Hello. Richard Pazdur, and I'm the director of the Oncology Center of Excellence at the United States FDA.

DR. STEVENSON: Dr. Donoghue?

DR. DONOGHUE: Good morning, everyone. I'm Martha Donoghue. I'm a pediatric oncologist and the associate director for Pediatric Oncology and Rare Cancers in the Oncology Center for Excellence at FDA.

DR. STEVENSON: Dr. Duke?

DR. DUKE: Good morning. I'm Elizabeth Duke. I'm a pediatric neuro-oncologist and clinical reviewer at the U.S. FDA.

DR. STEVENSON: Dr. Leong?

DR. LEONG: Good morning. My name is Ruby Leon. I'm an oncology pharmacist and clinical pharmacology team lead at the FDA.

DR. STEVENSON: Dr. Shord?

DR. SHORD: Good morning. I'm Stacy Shord. I'm a clinical oncology pharmacist, and I'm the

current deputy division director for the Division of Cancer Pharmacology II.

DR. STEVENSON: Dr. Wang?

(No response.)

DR. STEVENSON: Dr. Wang, you may be on mute.

(No response.)

DR. STEVENSON: Dr. Wang, if you can hear me, please unmute yourself, and introduce yourself by stating your name and affiliation for the record.

(No response.)

DR. STEVENSON: Okay. We'll come back to Dr. Wang.

Dr. Wessel?

DR. WESSEL: Hi. Good morning. I'm Kristin Wessel. I'm a pediatric oncologist and clinical reviewer at the U.S. FDA.

DR. STEVENSON: Thank you.

Dr. Wang, if you can hear me, please unmute yourself, and state your name --

DR. WANG: Hi. Yes. Hello. Good morning.

My name is Xiaofei Wang. I'm a clinical pharmacology reviewer in the Office of Clinical Evaluation, Office of Therapeutic Products of CBER. Thank you.

DR. STEVENSON: Thank you, everyone. I will hand it back to the chairperson.

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

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, 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 this meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you very much.

Dr. Stevenson will now read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. STEVENSON: Thank you.

The Food and Drug Administration, FDA, 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, FACA, of 1972. With the exception of the industry representative, all ODAC members and temporary members of the subcommittee are special government employees, SGEs, 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 ODAC members and temporary 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 that 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, ODAC members and temporary 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 a discussion of considerations related to dosage optimization of new drugs and biological products for pediatric patients with cancer. Dosage optimization is an integral aspect of oncology drug development and is important to maximizing the safety, efficacy, and tolerability of new drugs for pediatric cancers.

Unique considerations associated with dosage selection and optimization in pediatric oncology include variability in pharmacokinetic and

pharmacodynamic parameters by age and size; the need for age-appropriate formulations; potential for toxicities associated with long-term use; and the rarity of pediatric cancers. Representatives from the European Medicines Agency, the pediatric oncology investigator community, and the pharmaceutical industry have also been invited to present. 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 ODAC members and temporary members of the subcommittee, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all ODAC members and temporary members of the subcommittee 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. Jonathan Cheng is participating in this meeting as a non-voting industry representative, acting on behalf of

regulated industry. Dr. Cheng's role at this meeting is to represent industry in general and not any particular company. Dr. Cheng is employed by Bristol-Myers Squibb.

With regard to FDA's guest speakers, the agency has determined that the information to be provided by these speakers is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comments.

Dr. Samuel Blackman has acknowledged that he is the founder and head of research and development at Day One Biopharmaceuticals and member of the Scientific Advisory Board of Peel Therapeutics, and a member of Board of Directors of Presage Biosciences. He has also acknowledged holding a significant equity position in Day One Biopharmaceuticals, Inc., and has nominal equity in Peel Therapeutics, Presage Biosciences, Notable Labs, and Chimera Bio.

As guest speakers, Drs. Blackman, Fox, Karres, and Kholmanskikh will not participate in

subcommittee deliberations, nor will they vote.

We would like to remind ODAC members and temporary members of the subcommittee 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 participants to advise the subcommittee of any financial relationships that they may have regarding the topic that could be affected by the subcommittee's discussions.

Thank you. I will hand it back to the chairperson.

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

We will now proceed with FDA introductory remarks from Dr. Martha Donoghue.

FDA Introductory Remarks - Martha Donoghue

DR. DONOGHUE: Thank you, Dr. Pappo.

Good morning, and welcome to the 2023

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee meeting, and good afternoon or good evening to those of you who are joining us from Europe and elsewhere.

Many of us have heard the adage that it is important to give the right drug, to the right patient, at the right time. I would add to this that it is also important to give the right dosage of the right drug, to the right patient, at the right time. A few years ago, and in keeping with this, the Oncology Center of Excellence launched Project Optimus to educate, innovate, and collaborate with all stakeholders to move forward with a more modern dose-finding and dose-optimization paradigm across oncology that emphasizes selection of a dosage or dosages that maximizes not only the efficacy of a drug or biological product, but safety and tolerability as well.

I think most of us would agree that this is an important goal, but the question is how best to do this for our patients? Understandably, many

people have asked questions regarding how much and what type of information is needed to identify the optimized dosage of new drugs or biologics, and how to acquire this information in the most efficient way possible. Today, we will hear a variety of opinions and recommendations relating to dosage optimization, including why dosage optimization is especially important for pediatric patients, potential challenges to dosage optimization in pediatric oncology, and strategies to optimize the dosage of new drugs for pediatric patients with cancer.

The goal of today's meeting isn't necessarily to come away with a consensus on "the" best way to identify the optimized dosage of new drugs and biological products to treat pediatric cancers, but rather to have a better understanding of each other's perspectives to enhance communication and collaboration in our future efforts, understanding that a one-size-fits-all approach is not appropriate or possible.

I'd like to take this opportunity to thank

the members of the subcommittee for joining us today and for preparing for what should be a very interesting and vibrant discussion. I'd also like to express my sincere appreciation to the speakers who have kindly agreed to share their perspectives on this topic, including my colleagues from the European Medicines Agency, Dr. Karres and Dr. Kholmanskikh, as well as Dr. Beth Fox from St. Jude Children's Research Hospital, and Dr. Samuel Blackman, the founder of Day One Biopharmaceuticals. I'd also like to thank the speaker who will present during the open public hearing, as well as FDA staff, and all of you who are interested in this topic and have taken time out of your day to join us.

I'll turn things back to you, Dr. Pappo.

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

We will now proceed with three FDA presentations, starting with Dr. Kristin Wessel.

FDA Presentation - Kristin Wessel

DR. WESSEL: Thank you, Dr. Pappo, and

hello, everyone. My name is Kristin Wessel, and I'm a pediatric oncologist here at FDA. In this presentation, my colleague, Dr. Ruby Leong, and I will provide FDA's perspective on dosage optimization in pediatric oncology.

In this talk, we will first touch upon the importance of dosage optimization in pediatric oncology. Next, we will discuss unique aspects of pediatric oncology related to dosage optimization; common misconceptions and potential issues that can arise in pediatric oncology dosing; the different approaches to dosage optimization; and finally, opportunities for interactions with the FDA in order to reach agreement on the best approaches to dosage optimization for pediatric patients with cancer.

This slide provides some basic definitions of terms we will use throughout this talk and subsequent discussion. The term "dose" refers to the quantity of the drug received by a patient, such as 100 milligrams. Dosage refers to both the dose and the schedule, or the recommended interval

between doses and the duration of treatment such as 100 milligrams administered daily for up to one year. And finally, when we refer to an optimized dosage, we mean the dosage that can maximize the benefit-risk profile or provide the desired therapeutic effect while minimizing toxicity.

Now I'd like to address why we think it's important to discuss dosage optimization in pediatric oncology, specifically and at this particular time. First, dosage optimization is essential to achieve our common goal of prolonging life and ideally curing patients, while at the same time decreasing the risks associated with treatment.

This is paramount irrespective of whether the therapy is intended to treat adult or pediatric patients; however, identifying the optimized dosage is particularly crucial for pediatric patients in order to minimize their risk of incurring late effects of treatment that can adversely impact health and quality of life.

Second, there is increasing recognition that

the traditional more-is-better paradigm, that we have successfully implemented for decades with cytotoxic regimens, is not necessarily the best approach for patients. Recently, there has been a shift in the pediatric oncology drug landscape from cytotoxic chemotherapies to more targeted therapies such as kinase inhibitors, monoclonal antibodies, and antibody drug conjugates; and the dose response relationship with these targeted therapies often differs from that of cytotoxic chemotherapy.

And lastly, a public discussion regarding dosage optimization in pediatric oncology is especially important because of the complexity and potential challenges of dosage optimization in pediatric oncology due to the rarity of pediatric cancers, as well as other considerations specific to pediatrics that we will discuss shortly. Thus, a tailored and thoughtful approach is needed to best serve the needs of pediatric patients with cancer by optimizing dosages of cancer drugs without impeding drug development.

Typical dose-finding trials are designed to

identify the maximum tolerated dose of a product based on an evaluation of dose-limiting toxicities or DLTs. DLTs are generally severe treatment-emergent toxicities that occur within a short time of starting treatment, generally within the first cycle. This approach was developed for cytotoxic chemotherapies with limited drug target specificity and steep dose response relationships, as shown in the graph on the left.

As you can see, for cytotoxic drugs, there is generally a proportionate relationship between efficacy and toxicity. As shown on the graph on the right, the relationship between efficacy and toxicity for targeted agents is not always proportionate. Instead, as in this example, there can be a range of doses for which increasing the dose does not increase efficacy but does result in a steep increase in toxicity; and therefore a lower dose may provide the best benefit-risk balance for this product.

This slide highlights some other key differences between cytotoxic chemotherapy and

targeted drugs that support implementing more modern approaches to identify the dosage to carry forward into later trials. Cytotoxic chemotherapies are typically given for a fixed number of cycles or a short duration of treatment. Many of the serious toxicities -- for example, myelosuppression -- are predictable and occur relatively early. And while late effects of treatment are an important consideration, other symptomatic toxicities such as nausea and diarrhea can resolve with time off of treatment.

In contrast, the different dose response relationship for many targeted therapies means that the maximum tolerated dose may not be identified with typical dose-finding trials. Additionally, in contrast to cytotoxic chemotherapy, treatment with targeted therapies may last for months to years with serious toxicities potentially occurring after several months of treatment. And when treatments are given on a continuous basis, as we see particularly with orally administered targeted therapies, evaluation of chronic but lower grade

toxicities becomes more important. We have heard from patients that long-term tolerability of oral targeted therapies can be a serious issue.

Diarrhea is an interesting example of the importance of a chronic low-grade toxicity that is not typically considered a dose-limiting toxicity. Here we see the CTCAE grading terminology for grades 1 to 5 diarrhea, and while we can all agree that grades 3 to 4 diarrhea would be a DLT, grades 1 to 2 diarrhea, or up to 6 stools per day over baseline, would not be typically considered a DLT but would be difficult to tolerate if it persists for weeks, or even months to years.

This underscores the need to include lower grade toxicities in our evaluation of dosages to be carried forward in clinical trials because they can negatively impact a patient's quality of life. For pediatric patients, they can also affect the caregiver. If a child can't attend school because of grade 2 diarrhea, a parent may not be able to attend work, which can lead to financial toxicity and other socio-economic effects.

To further illustrate the importance of dosage optimization, I will now discuss a real-world example from adult oncology. In 2019, the FDA granted accelerated approval to trastuzumab deruxtecan, a HER2-directed antibody and topoisomerase inhibitor drug conjugate for the treatment of HER2-positive breast cancer at a dosage OF 5.4 milligrams per kilogram every 3 weeks. At the time, interstitial lung disease pneumonitis was identified as an important safety signal in patients with breast cancer, resulting in a boxed warning.

In 2022, trastuzumab deruxtecan also received accelerated approval for the treatment of HER2-mutant, non-small cell lung cancer based on the results of two studies. The initial trial in non-small cell lung cancer, DESTINY-Lung01, was a single-arm trial with objective response rate as the primary endpoint. The sponsor selected a dosage of 6.4 milligrams per kilogram every 3 weeks, which had promising anti-tumor activity with an objective response rate of 55 percent in

91 patients; however, interstitial lung disease occurred in 26 percent of the patients and resulted in 2 deaths.

Based on discussion with FDA, the sponsor then conducted the study DESTINY-Lung02, a randomized dosage optimization trial comparing 6.4 milligrams per kilogram to 5.4 milligrams per kilogram every 3 weeks. ORR and duration of response were found to be similar between the two groups; however, the incidence of interstitial lung disease and pneumonitis was 14 percent at the higher dose versus 6 percent at the lower dose. Therefore, 5.4 milligrams per kilogram every 3 weeks was determined to be the recommended dosage for patients with non-small cell lung cancer.

This example shows how dosage optimization can successfully occur prior to approval in order to improve the benefit-risk balance for patients. However, we do acknowledge that this exact trial design may be difficult to execute in the pediatric setting, given smaller numbers of patients.

Now I will discuss a real-world example of

dosage optimization in pediatric oncology. In 2021, the FDA approved a supplemental indication for crizotinib for the treatment of pediatric and young adult patients with relapsed or refractory systemic anaplastic large-cell lymphoma, the first approval for this disease in pediatric patients. Approval was based on the children's oncology group study, ADVL0912, a single-arm does escalation and dose expansion study, which enrolled 26 patients.

Efficacy was assessed by overall response rate and duration of response. 280 milligrams per meter squared orally twice daily was the maximum tolerated dose carried forward to the expansion cohort. It was noted that ORR was similar at both dose levels with overlapping confidence intervals; however, the small number of patients led to difficulty in making comparisons.

While the exposure-efficacy relationship appeared flat for ORR and complete response, the exposure-safety relationship suggested an increased incidence of neutropenia and vision disorders with higher exposures. We ultimately decided, along

with the sponsor, to issue a postmarketing commitment to assess efficacy and safety at a lower dose that might provide a better benefit-risk profile for pediatric patients with systemic ALCL. A goal moving forward is to encourage this type of dosage optimization prior to approval so that pediatric patients can benefit from receiving an optimized dose and avoid excess toxicity as soon as possible.

In the next two slides, I will contrast the traditional dosage selection strategy with an example of an updated dosage selection strategy. Shown here is the Rolling 6 design that is commonly used in pediatric oncology studies. This simple rule-based design has been used to identify the maximum tolerated dose because this design avoids exposing too many patients to subtherapeutic doses while preserving safety and facilitating more rapid accrual.

With this design, the dose-limiting toxicity assessment window is relatively short, for example, a single chemotherapy cycle. Adverse events that

occur beyond the short time frame are not considered when identifying the MTD, nor are lower grade chronic toxicities. These data may then not be considered when selecting the recommended phase 2 dose that will be taken forward to subsequent phases of study.

This is important because even if a drug is deemed tolerable in a dose escalation study with a small number of patients, when carried forward, patients may require dosage modifications to manage adverse reactions or be exposed to unnecessary toxicities. If the dosage was optimized earlier, there would be a better balance between benefit-risk for patients.

This slide provides a high-level example of an alternative approach to dosage selection. In the dose escalation study, more than one dosage may be chosen to evaluate further in order to optimize the dosage. In choosing the dosages to carry forward, it is important to consider the totality of pharmacokinetic, pharmacodynamic, efficacy, safety, tolerability, and available adult data. In

this example, two dosages will be further studied to select an optimized dosage to be evaluated in a registrational trial.

Again, this is just one example of a method that can be used for dosage optimization. There are a number of other possibilities, including investigating two dosages in an expansion phase of the same trial and incorporating designs to selectively backfill dosing cohorts to acquire the information needed.

Given the rarity of pediatric cancers, it is worth emphasizing that it is possible to acquire the information needed to identify the optimized dosage with a relatively small number of patients and by leveraging available adult data to inform the pediatric dosage. Other approaches such as pediatric extrapolation and modeling and simulation should be considered. We are happy to discuss the best path forward for a given development program in order to facilitate expeditious drug development.

We know that there are several unique

considerations in pediatric oncology that can influence the approach to dosage optimization. Different dosages may be needed across the span of pediatric age groups for which a drug may be indicated due to potential differences in pharmacokinetics and pharmacodynamics based on developmental changes and body size; so we should consider whether different dosing strategies are needed based on age, as well as appropriate PK and PD sampling schedules.

For oral drugs, we need to consider a patient's ability to swallow, palatability, and food effects. We also need to consider the potential for long-term effects on growth, cognition, sexual development, and other late effects for some targeted therapies. And finally, because all pediatric cancers are very rare, it is especially important to be thoughtful about how we integrate dosage optimization into clinical development. Arriving at this strategy should be a collaborative effort in which we would very much like to engage.

This slide provides a summary of information that can be used to identify the optimized dosage, or dosages, for a pediatric oncology product. The totality of information, including the relationship between dosages; exposure; activity/efficacy, safety; tolerability; and pharmacokinetics and pharmacodynamics should be evaluated throughout drug development. In addition, as Dr. Leong will describe later, extrapolation from adult data and modeling and simulation can often be employed to facilitate dosage optimization. Finally, formulation considerations are important to think about during the clinical development of orally administered drugs intended to treat younger pediatric patients with cancer.

I will now take some time to address a few misconceptions some people may have regarding dosage optimization in pediatric oncology. Currently, the majority of pediatric cancer drug development occurs with drugs that are being developed for the treatment of adult cancers, and in these cases, we have the opportunity to leverage

available data from the adult population to inform pediatric dosing. However, one misconception is that identification of the optimized dosage in adults is needed prior to initiation of trials in children.

We would like to emphasize that this is not necessary and not the approach we recommend since we would like drugs that have the potential to benefit pediatric patients studied as early as possible. Additionally, in cases where the drug target is not relevant to an adult cancer, the first-in-human trial can occur in pediatric patients when there is sufficient scientific justification and preclinical information to support this approach.

Next, there is a question of whether the recommended phase 2 dose for monotherapy should be established in pediatrics prior to initiation of trials evaluating combination therapies, and this is not always the case. Early data from monotherapy can help support an appropriate starting dosage for combinations, taking into

account the potential for overlapping toxicities and drug interactions. Additionally, there are situations when the drug is not expected to have sufficient activity by itself to warrant extensive evaluation as monotherapy.

Finally, we acknowledge there is a concern that dosage optimization will not be feasible in pediatric and other rare cancers. We believe that it is possible to incorporate principles of dosage optimization without impeding pediatric drug development. We understand the need for flexibility when warranted and that there cannot be a one-size-fits-all approach. Dosage optimization may look different depending on the population and the specific development program.

Now, my colleague, Dr. Ruby Leong, will discuss clinical pharmacology considerations for dosage optimization.

FDA Presentation - Ruby Leong

DR. LEONG: Thank you, Dr. Wessel.

My name is Ruby Leong, and I am a clinical pharmacology team lead at the FDA. Following on

the misconceptions in pediatric oncology dosing presented by Dr. Wessel, for the next few slides, I will present potential issues encountered in pediatric oncology dosing. The first potential issue encountered during pediatric oncology drug development is escalating to the maximum tolerated dose and selecting the dose based on only short-term safety data following the cytotoxic chemotherapy and PD paradigm. As Dr. Wessel mentioned before, we should be moving away from the more-is-better mindset associated with cytotoxic chemotherapy.

All available data, including adult clinical data, and modeling, and simulation, should be considered to select a pediatric dosage. For pharmacokinetics and pharmacodynamics, the sampling plan should be appropriate for age and size. Modeling tools can be used to optimize the PK sampling schedule and to conduct PK/PD analysis to inform a target dosage range with pharmacologic activity. The activity, efficacy, and safety observed in adults, along with the dose and

exposure-response relationships, should be considered to inform pediatric dosage selection. Short and long-term safety monitoring in pediatrics as appropriate may provide additional supportive data. Assessment of tolerability using patient-reported outcome data should also be considered when available.

FDA recommends consideration of early incorporation of clinical outcome assessments to inform pediatric dosage optimization. Tolerability assessments can provide additional data that is complementary to traditional safety information. The NCI's Pediatric PRO-CTCAE is one example of a tool that can incorporate the degree to which treatment-related symptomatic and non-symptomatic adverse events can affect the ability or desire of a patient to adhere to the treatment regimen. Relevant items from the Pediatric PRO-CTCAE could be selected specific to the population and investigational product being evaluated.

The second issue we sometimes see occurs with proposals to escalate dosing and pediatrics

beyond the adult RP2D in the absence of adequate scientific justification for monotherapy or combination therapies. For example, for a study investigating a new drug in combination with standard chemotherapy, the sponsor proposed a pediatric body weight adjusted dose of the drug in combination that was higher than the adult equivalent single-agent recommended phase 2 dose. Due to potential overlapping toxicities with the combination, approaches to minimize overlapping or compounding toxicities should be considered such as reduction of the starting pediatric dose to lower than the adult equivalent single-agent dose.

The third issue that we have sometimes encountered is that no dosage exploration is planned at all, where only one dose level was being evaluated. In general, we recommend exploration of more than one dosage to further understand dose and exposure relationships with efficacy and safety.

The fourth potential dosing issue is the lack of an age-appropriate formulation, including lack of appropriate strengths to cover dosages

needed for the intended age range. Manipulating solid dosage forms, such as crushing tablets or opening capsules, and administering with a vehicle to make an extemporaneous preparation can also impact drug exposure, leading to safety or efficacy concerns.

Early attention should be given to the development of an age-appropriate formulation and how it should be administered with regards to food. If the drug can offer an advantage to pediatric patients, we would not want to delay investigation until a pediatric formulation is developed.

There are cases where extemporaneous preparation is reasonable while the age-appropriate formulation is being developed; however, potential differences in exposure with the extemporaneous preparation should be considered to select an appropriate dosage and minimize effects on efficacy or safety of the drug. Finally, a relative bioavailability study of the pediatric and adult formulations should also be conducted, typically in adults as early as possible.

Given the potential dosing issues presented in the previous slides, I will now present some of the approaches that may help dosage optimization, including leveraging adult data, pediatric extrapolation, and applications of model-informed drug development or MIDD.

I mentioned the importance of fully utilizing adult data to inform pediatric dosing in cases like the first scenario in this slide, where clinical data in adult patients with cancer are available. When utilizing the adult experience to inform dosage selection for pediatric patients, we generally consider whether the adult dosage is adequately supported and whether the dosage identified for adults is for a cancer type that also occurs in pediatric patients or whether the tumor types are different

If a recommended phase 2 dose or optimized dosage has been identified for adults, the totality of the adult PK/PD, efficacy, safety, and tolerability data can be leveraged to inform dosing in pediatric studies, and there may be less dose

finding needed in pediatrics. If an adult recommended phase 2 dose has not been identified, or for first-in-human pediatric studies, we consider the available information; for example, clinical PK and safety or non-clinical data that can be used to inform pediatric trial design and safety risks. As I will discuss in more detail in a few minutes, modeling and simulation approaches can be helpful for all these scenarios.

This slide summarizes the high-level concepts of the approach to pediatric extrapolation outlined in the ICH E11A Pediatric Extrapolation guidance, which is more relevant to the common scenario of cancer drugs being developed for the treatment of adult and pediatric patients with cancer, with at least some adult data accumulated prior to investigation in pediatrics.

The extrapolation approaches and potential study designs depend on a continuum of the level of evidence, or prior knowledge, and confidence level and similarity of disease and response to treatment between adults and pediatrics. This framework also

highlights that even in scenarios where the pediatric and adult cancers and response to treatment are highly similar, we still need high-quality data to support the pediatric development plan.

We have mentioned modeling and simulation often in this presentation. Model-informed drug development, or MIDD, approaches may play an important role in pediatric drug development and can be used to support pediatric extrapolation. Model-informed approaches can also be used for pediatric dosage optimization by incorporating information on pediatric ontogeny; identifying important covariates such as weight, body surface area; and also predicting PK in various age groups. Model-informed approaches can be used to fill in gaps in knowledge by leveraging prior information from adults or other drugs from the same class, and known exposure-response relationships for efficacy and safety.

Another utility of modeling is to inform clinical trial design, including appropriate

dosages for evaluation across the pediatric age range, sample size, an optimal PK or PD sampling for pediatric patients. A variety of statistical and other quantitative tools such as PK/PD, physiologically based pharmacokinetic modeling, and quantitative systems pharmacology models can also be utilized.

I will now turn it back to Dr. Wessel to conclude the presentation.

FDA Presentation - Kristin Wessel

DR. WESSEL: Thank You, Dr. Leong.

We want to highlight opportunities for interactions with the FDA to obtain feedback on dosage optimization for a given development program. We encourage discussions early and often with the FDA for input on dosage optimization strategies throughout the drug development process. These discussions can begin at the pre-IND stage, at the end of a phase 1 or 2 meeting, or in a Type D meeting, which is intended to focus on a narrow set of issues and can be used to discuss dosage optimization at any point along the drug

development pathway.

Public meetings and workshops are also opportunities for stakeholders to interact with FDA. FDA will co-host a workshop with the International Society of Pharmacometrics in October on dosage optimization for oncology drugs, specifically using modeling and simulation to evaluate the effects of intrinsic and extrinsic factors.

And finally, the FDA and European Medicines Agency, or EMA, collaborate in various ways to discuss topics related to the pediatric development programs and to reach alignment on advice for sponsors. These collaborations include pediatric cluster teleconferences, including international regulatory agencies; a common commentary process through which FDA and EMA provide informal and non-binding comments to sponsors on pediatric development plans; and formal parallel scientific advice, which is a sponsor-initiated interaction through which FDA and EMA can discuss the development program together prior to providing

feedback.

In summary, timely dosage optimization is important to ensure the best possible quality of life for children with cancer receiving targeted therapies. We believe incorporation of dosage optimization and pediatric clinical trial design will minimize the potential for dosage interruptions and discontinuations due to toxicity and will minimize the chance of late effects.

To arrive at the optimized dosage, the totality of data and approaches such as pediatric extrapolation and model-informed drug development should be considered. We acknowledge the need for flexibility and that there is no one-size-fits-all approach to dosage optimization in pediatric oncology. Early discussions with FDA are recommended to facilitate integration of dosage optimization for seamless drug development.

This slide provides some dosage optimization resources. I again wanted to highlight Project Optimus through the Oncology Center for Excellence, which Dr. Donoghue mentioned in her introductory

remarks, and we encourage you to visit the website for more information and resources. And lastly, this slide provides resources specific to pediatric development and model-informed drug development.

This concludes our presentation. Thank you very much for your time and attention, and I will now turn it over to my colleague, Dr. Xiaofei Wang, for the next presentation.

FDA Presentation - Xiaofei Wang

DR. WANG: Thank you, Dr. Wessel.

Good morning, everyone. My name is Xiaofei Wang. I'm a clinical pharmacology reviewer in the Office of Clinical Evaluation, Office of Therapeutic Products, Center for Biologics Evaluation and Research. Today, I will talk about dose optimization considerations for chimeric antigen receptor, CAR T-cell products.

This is an outline of my presentation. I will first have a brief overview of CAR T-cell therapy, the differences between CAR T-cell therapy and conventional therapies, and then I will discuss dose considerations in the development of

CAR T-cell therapy and our experiences of dose-response relationships for approved CAR T-cell therapies. At the end, I will talk about the dose optimization principles in the development of CAR T-cell therapy. To facilitate the development of CAR T-cell products, I will also provide some regulatory resources.

CAR T-cell therapy is an ex vivo genetically modified T-cell immunotherapy targeting cell surface antigens. CAR T cells are living drug products which proliferate during the manufacturing process. As shown in the right graph, after infusion, CAR T cells bind to the target antigen and get activated, starting expansion and differentiation. Activated T-cell signaling results in lysis of tumor cells, cytokine signaling, and stimulation of bystander immune cells.

This slide shows the general procedure of CAR T-cell therapy. I'm going to use autologous CAR T-cell therapy as an example. Autologous CAR T-cell therapy uses the patient's own T cell to

manufacture the CAR T cells that they will receive. First, T cells are collected by removing peripheral blood from patients, which is called apheresis. The collected T cells go through genetic modification and expansion to obtain sufficient T cells, expressing chimeric antigen receptor. Patients receive CAR T cells through intravenous infusion.

In general, to help CAR T-cell in vivo expansion and enhance efficacy, patients receive lymphodepletion conditioning prior to administration of CAR T cells. After infusion, CAR T cells distribute and bind to target antigen and initiate activation signaling to kill cancer cells and stimulate immune responses against cancer cells.

This slide compares CAR T-cell therapy and conventional therapies. Regarding active drug substance, CAR T cells are ex vivo genetically modified T cells. Unlike the active drug substance of conventional small molecule or antibody-based therapies, CAR T cells are living drugs.

CAR T-cell products contain different T-cell subsets. The composition of autologous CAR T-cell products is unique for each patient, while conventional therapies usually have a fixed drug composition, single active pharmaceutical ingredient, or fixed-dose combination.

As I mentioned before, CAR T-cell therapy is given by infusion, mostly by intravenous infusion. There are various routes of administration for conventional therapies. For CAR T cells, the therapeutic effects may be achieved via single-dose treatment, for example, autologous CAR T cells for hematological malignancies. In general, therapeutic effects may be achieved by multiple-dose treatment for conventional therapies.

The conventional absorption distribution, metabolism, and excretion concepts, which apply to pharmacokinetics of conventional therapies, do not apply to the pharmacokinetics of CAR T cells. This is because CAR T cells are living drugs. Cells proliferate in vivo after administration; therefore, the mass balance concept does not apply

either.

There are two types of CAR T cells, autologous CAR T cells and allogeneic CAR T cells. Autologous CAR T cells are made from a patient's own T cells. The drug product composition is unique for each patient. This may increase risk of potential therapy delay or manufacturing failures, while allogeneic CAR T cells are made from a healthy donor's T cells. It's a universal, off-the-shelf product. This decreases risk of potential therapy delays or manufacturing failures.

Because autologous CAR T cells are made from a patient's own T cells, there's no concern of graft-versus-host disease, and long-term persistence is observed for autologous CAR T cells; however, for allogeneic CAR T-cell products, due to potential immune responses, graft-versus-host disease and the long-term in vivo persistence are potential concerns.

In August 2017, FDA approved the first CAR T-cell therapy, Kymriah, for patients up to 25 years of age with B-cell precursor acute

lymphoblastic leukemia. This is currently the only approved CAR T product for pediatric patients. Since 2017, FDA has approved six CAR T-cell products. The first four are anti-CD19 CAR T-cell products and the last two are anti-BCMA CAR T-cell products.

Now, let's talk about dose considerations in clinical development of CAR T-cell therapy. The starting dose in first-in-human studies is generally based on preclinical and available clinical experiences of the same product or similar CAR T products. For autologous CAR T-cell therapy, especially administered through intravenous infusion, we do not recommend the intra-subject dose escalation. I will talk about reasons later when I discuss considerations for repeat dosing.

Various dosing regimens have been reported. In general, single-dose IV infusion has been used with autologous CAR T cells for hematological malignancies. Single and repeat doses have been reported for both autologous CAR T cells indicated for solid tumors and allogeneic CAR T cells.

There are some considerations for repeat dosing. First of all, lymphodepletion is myelosuppressive. Multiple rounds of lymphodepletion may raise potential safety concerns. Secondly, we have observed substantial lower CAR T-cell expansion after repeat dosing compared to the CAR T-cell expansion after the initial dose. This may be due to antigen escape and T-cell exhaustion.

As I mentioned earlier, CAR T-cell therapy is a living drug that is composed of different subsets of T cells. Different T-cell subsets have different expansion capacity and different functionality; therefore, product characteristics such as composition of different T-cell subsets and the status of differentiation of T-cell subsets may affect the in vivo expansion and clinical outcomes.

To improve CAR T-cell in vivo expansion, patients usually receive lymphodepletion conditioning prior to receiving CAR T-cell treatment. Lymphodepletion increases CAR T-cell expansion and persistence by removing cytokines

[indiscernible] and eradicating immunosuppressive elements such as regulatory T cells. Different indications may require different doses of CAR T cells to achieve stratified safety and efficacy.

In addition, a different indication may require a different route of administration. For example, intracavitary administration is used for central nervous system cancer, and the differences between intracavitary and regular IV infusion should be considered for dose selection.

As general development of conventional therapies, the exposure-response relationship usually provides important information in dose optimization. Clinical safety and efficacy profiles are always critical in dose selection, especially in the situation that there's no evident dose-response relationship for certain CAR T products.

Currently, we have limited experiences with developing CAR T-cell therapy for pediatric patients with cancer. There's only one approved CAR T product indicated for treatment of pediatric

patients, Kymriah for the treatment of patients up to 25 years of age with refractory B-cell precursor acute aplastic leukemia. The product labeling includes a wide range of recommended dosing for this product, 0.2 to 5 million CAR-positive viable T cells per kg of body weight for patients 50 kg or less, or 10 to 250 million CAR-positive T cells for patients more than 50 kg. This is based on considerations of lack of evidence of dose-response relationship in clinical trials and manufacturing feasibility.

For conventional therapies, data from adults is generally used to inform pediatric dosing. For CAR T-cell products, data from adults may also inform dosing in children. Therefore, inclusion of adolescents in adult trials is encouraged if scientifically justified; however, in many cases, children and adults have distinct biologics of malignancies. The overlap for cancers and antigens of interest between children and adults is very limited.

To address this issue, early phase clinical

studies may need to enroll both children and adults. Unlike doses of CAR T-cell products in adults with both flat dose and body weight or body surface area-base dosing, we generally recommend the body weight or body surface area-based dosing rather than flat dosing for pediatric patients.

This slide illustrates that the dose exposure relationship of CAR T-cell products can vary. As shown in the left graph of this slide, there's no evident dose exposure-response relationship observed for Breyanzi, an anti-CD19 CAR T product. In contrast, we observe a positive dose exposure response for Abecma, an anti-BCMA CAR T-cell therapy. Because of the heterogeneity of autologous CAR T-cell products, we see high intra-subject variability and overlapping of the exposure across different dose levels.

This slide shows the exposure response relationships for efficacy that are typical for the CAR T-cell products. In general, CAR T-cell exposure shows [indiscernible] risk factor efficacy. This slide shows exposure-response

relationship for safety perspective. Subjects with cytokine release syndrome had higher CAR T-cell exposure compared to subjects who did not experience cytokine release syndrome or severe cytokine release syndrome.

In summary, dose optimization is critical in the development of CAR T-cell therapy, especially for hematological malignancies. Sometimes a single dose may achieve intended therapeutic effect. In light of the single-dose strategy, ensuring patients receive the best, most optimized dose is especially important. While dose optimization for CAR T-cell products is challenging, for autologous CAR T products, exposure profiles overlap across different doses due to product heterogeneity.

The general principles of oncologic drug product dose optimization, talked in Dr. Wessel and Dr. Leong's presentation, also apply to CAR T-cell therapy. Dose optimization is based on the totality of safety, efficacy, and pharmacokinetic/ pharmacodynamic data. Due to the complexity of dose optimization of CAR T-cell therapy, we

encourage investigators to communicate with FDA in the early phase of clinical development.

The development of CAR T-cell therapy is challenging, and dose optimization is very critical. This slide lists some FDA guidances for cell and gene therapy product development. This is the FDA guidance for dose optimization. The general principles and strategies also apply to CAR T-cell therapy. Thank you.

Clarifying Questions

DR. PAPPO: I would like to thank Drs. Wessel, Leong, and Wang for their excellent presentations.

We will now take clarifying questions for the FDA presenters. Please use the raise-hand icon to indicate that you have a question, and please 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 to the next panel member.

I see several questions already. We're going to start with Dr. Steve DuBois.

DR. DuBOIS: Thank you, Dr. Pappo. Steve DuBois, Dana-Farber/Boston Children's. Actually, I have questions for all presenters, but maybe I'll just ask two of the questions that I have.

For Dr. Wessel, can you give us a sense of the range of sample sizes that have been included in some of the dose optimization, sort of randomized dose optimization studies, just to give us maybe some bookends on how that's been done?

Then for the last presenter, I'm struggling a little bit with the CAR T exposure because, of course, the dose that's administered doesn't always translate into the exposure over time of the

T cells because they can expand. So I wonder if you have thoughts on how that can be dealt with or conceptualized in terms of dose optimizing. Thank you.

DR. WESSEL: Hello. This is Kristen Wessel with FDA. I'll start by answering the sample size ranges question. I think most of this comes from the adult setting, but most sample sizes have included maybe 20 to 50. I will say that in the pediatric setting, the purpose of randomization is not necessarily to power a statistical comparison; it's more to ensure that patient characteristics are evenly balanced across groups.

I do want to allow Dr. Mirat Shah, who is lead in Project Optimus, to respond to this question as well.

DR. SHAH: Hi, everyone. My name is Mirat Shah. I'm a breast and gynecologic oncologist at FDA and also one of the co-leads for Project Optimus. I just wanted to provide additional context for this question. I think this question of randomization -- why, how many, when -- is

incredibly important to this entire discussion.

Just stepping back a bit, I think we all understand that understanding dose response is critical for dosage optimization, and the reason randomization is something that we recommend in some settings is because we I think it's a particularly powerful tool to understand dose response or attempt to balance the known and unknown factors that might be present in different patient populations receiving the different dosages, and to try and limit the influence of confounders on our interpretation of dose and response relationships.

That being said, it's not something that we recommend just to recommend, so if we think that it's unlikely to be feasible in a certain setting, or unlikely to be informative in a certain setting, or may not even be needed because so much other data exists that can be leveraged, then we wouldn't necessarily recommend it. And I think the questions of sample size really depend on the specifics of the scenario, which is why, as

Dr. Wessel mentioned, we welcome these early interactions that are collaborative between sponsors and regulatory agencies to try and understand the different approaches that can be used and provide advice. I'll pause there.

DR. DuBOIS: Thank you. That was very helpful.

Then maybe Dr. Wang for the question about exposure, like dose exposure for T cells that can expand.

DR. WANG: Hello. This is Xiaofei Wang, clinical pharmacology reviewer. Regarding the exposure of T cells, currently with dose exposure response, we have observed different dose exposure responses. For certain drug products and also for certain indications, we note that there's no evidence for dose exposure response; however, for certain others we receive, we notice positive dose and responses.

Also, these may impact by the different indications also due to the heterogeneity of autologous CAR T-cell products. However, in

general, regarding the exposure response, we generate noticed a higher exposure associated with better efficacy. Thank you.

DR. DuBOIS: Thank you. Nothing further for me, Dr. Pappo.

DR. PAPPO: Thank you very much.

Dr. Malcolm Smith is next.

DR. SMITH: Thank you. I have a question for Dr. Wessel, and it relates to slide 5 in her presentation. The question, in general, is what are the classes of agents within the group of what we call molecularly targeted agents for which a broad therapeutic window can be expected, and for which you might find meaningful changes in doses that could be made without compromising anticancer effort?

ALK is an example. Yes, there's a range of doses that are effective. Imatinib would be another one; many of the targeted kinase inhibitors for which there are gene fusions or kinase mutations. But then we have other agents that we call targeted as well, like MEK inhibitors, and the

MEK inhibitors would be an example for which the preclinical in vivo data shows that there's a dose-response relationship that extends well beyond the drug exposures that can be tolerated in people. So we would love to give more, but we can't because of skin toxicity, because of other toxicities that arise, and other agents, HDAC inhibitors, MDM2 inhibitors, LSD1, a range of agents for which the dose exposure relationship from preclinical studies extends beyond what's tolerable in the clinic.

So my general question is, is there recognition of this distinction in targeted therapy agents; and if so, how is it dealt with? Because presumably for an agent like a MEK inhibitor, you use the highest dose that would be tolerated in patients, being careful to define what tolerability is and including chronic dosing. So again, is there recognition of this distinction; and if so, how is it dealt with?

DR. WESSEL: Hi. Yes. This is Kristin Wessel with FDA. Thank you so much for the

question. I will acknowledge that we do definitely agree that the toxicity and efficacy relationship isn't going to be exactly the same for all targeted agents, and we're trying to find that sort of intersection on the curve where we maximize efficacy without increasing toxicity and, yes, that can look different for different classes of agents. So it really depends on the specific drug and the development program. So this is kind of a general slide for illustrative purposes, but we do recognize that not every curve of toxicity and efficacy for every targeted drug is going to look exactly like this.

I'll give my FDA colleagues an opportunity to elaborate, if they wish to, on that question.

(No response.)

DR. SMITH: Okay. Thank you.

DR. PAPPO: Next is Dr. Julia Glade Bender.

DR. GLADE BENDER: Thank you. Julia Glade Bender from Memorial Sloan Kettering. I have a question that I think is directed to both Dr. Wessel and Dr. Leong, which is what is the role

that therapeutic drug-level monitoring might have in optimizing dose? Because with several of the targeted agents, we've observed that there really isn't a dose exposure relationship necessarily; there's a lot of intra-patient variability. So is there a role for therapeutic drug monitoring in order to optimize dose?

(No response.)

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

DR. DONOGHUE: Sorry. This is Martha Donoghue, and I'll just start off with that answer to that excellent question. The quick answer is that there certainly is a role for therapeutic drug monitoring and dosage optimization. I think, based upon my experience, sometimes it's difficult to get that data in a timely way in order to inform drug development as it proceeds, although certainly, if it's available, I think it can provide very important information to guide our approach to dosage optimization.

Your point about intra-patient variability is also well taken in that if there is a drug that

has a large degree of intra-patient variability, we may need to think about dosing strategies where we're individualizing dosing for patients, although that's not typically the norm.

I am wondering if any of my clinical pharmacology colleagues would like to weigh in as well on this.

Dr. Shord, do you have any thoughts on this or do you think I covered it?

(No response.)

DR. GLADE BENDER: Dr. Pappo, may I ask a second question?

DR. PAPPO: Yes, of course.

DR. GLADE BENDER: The second question was actually probably directed at Dr. Wessel, which was, again, the idea -- I believe you mentioned that a randomized dosage question could be incorporated in a registration trial, and as we move towards more seamless trial designs and fit-for-filing designs, I wonder what that looks like; and is the dose optimization question part of the efficacy question, and if, in fact, one of the

dosages is less efficacious, how is that addressed by the trial?

DR. WESSEL: Thanks for the question. I think I'll emphasize that we like to start these discussions on designs of trials in the very early stages, and we do acknowledge that maybe not every registrational trial will incorporate a randomized dosage optimization design. This can be done in other ways in pediatrics, and we acknowledge that it may be difficult to accomplish.

I think, emphasizing again, we need to look at the totality of the data throughout drug development. If there is a less efficacious dose, I think it's a matter of looking at the overall risk-benefit of the drug profile. For example, we would advocate a Bayesian design, in that case where an arm can be dropped if it's not as efficacious or safety is clearly worse, if we were in the scenario that you mentioned.

I'll let, I think, some of my colleagues chime in on that because I think there might be other thoughts.

DR. SHAH: Hi, everyone. I can provide some comments on this excellent question also. I think, as Dr. Wessel and my other colleagues have alluded to, the specifics do depend on the scenario, but I can outline some different scenarios that might be illustrative and kind of broad strokes.

So it really depends on the specific development program, but in a situation where the investigational product was being compared to standard-of-care control arm, and there were multiple dosage arms for the investigational product, there would be a need for a strong type 1 error control, and we would really want input from our statistical colleagues on that design. However, the overall assessment of efficacy for the investigational product to the standard-of-care control arm could be separated from, perhaps, an earlier interim assessment of the overall risk-benefit of the different investigational product dosages being evaluated to perhaps drop one of those arms.

In other situations, where a randomized

trial comparing the investigational product to a standard-of-care control arm would not be the approach forward, perhaps something like a single-arm trial would be what would be used for approval. In that situation, still patients can receive multiple dosages of the investigational products, and we can look at the totality of efficacy, and safety, and tolerability information generated to inform our assessment. But yes, I just wanted to provide that additional context to a really good question.

DR. GLADE BENDER: Thank you.

DR. PAPPO: Thank you.

I'd like to allow one additional question, and then the other ones, Drs. Balis and Mody, we will have additional time after lunch where we can ask additional clarifying questions.

Dr. Laetsch, please ask your question.

DR. LAETSCH: Thank you, Dr. Pappo. My question was similar to Dr. Glade Bender's, but I'll address it to Dr. Wang about, again, intra-patient variability of CAR T-cell exposures.

As already been discussed, clearly, these are autologous products, so there are differences there. There are also differences in patient disease burden and target, which may drive differences in expansion.

So again, I wonder how the FDA thinks about trial designs such as fractionated or CAR dosing, that smaller doses are given serially and stopped if there's excess toxicity, or other ways of individualizing dose for individual patients when there is expected to be high degrees of variability.

DR. WANG: Yes. Thank you very much. That's a very good question. I think this is an excellent question and a point made here. In addition to the product characteristics, like heterogeneity [indiscernible], also there are many other confounding factors that may impact the CAR T-cell expansion, including the tumor burden.

We have seen many different dosing strategies to mitigate the risks of CAR T-cell therapy, including this splitting dose. But now I

have to say, we have not reached a conclusion regarding whether the splitting dose is better than a single dose because we have seen different experiences. Some investigators, even later on, they have some preliminary evaluations comparing the splitting dose and one single dose. Sometimes they didn't find a substantial difference, and then they started moving on with a single dose. However, some investigators, they believe the splitting dose might have a better safety profile, and they continue proposing the splitting dose. Now, we are still at a stage of collecting data and the experiences regarding this.

Also, I'd like to ask my colleague, Dr. Najat Bouchkouj, if she would like to elaborate for this. Thank you.

DR. BOUCHKOUJ: Sure. Thank you, and thanks for the excellent question. This is Najat Bouchkouj. I'm a pediatric oncologist at the FDA. I just want to echo what Dr. Wang just had mentioned, that we are right now still in the early phase in terms of dose optimization for CAR T-cell

therapy in clinical trials. We are at the stage where we are still gathering data. We are encouraging early communications with the FDA in terms of study designs, where we can optimize the optimal dosage for these therapies, and to take into consideration the efficacy and safety as well, because as mentioned, split dosing has been proposed by several investigators, and ultimately what we want is just to collect data and see if these approaches are going to be informative in the future. I hope that answered that question as well.

DR. LAETSCH: Yes. Thank you very much.

DR. PAPPO: And again, we will have additional time for more clarifying questions after the open public hearing session of the meeting.

We will now proceed with the first guest speaker presentation from Dominik Karres, followed by Dr. Olga Kholmanskikh.

Guest Speaker Presentation - Dominik Karres

DR. KARRES: Thank you very much. My name is Dominik Karres. I work at the Paediatric

Medicines Office at the European Medicines Agency, and I would like to thank you very much for this kind invitation, giving us the opportunity to provide the European perspective and considerations related to dose optimization of new drug and biological products for pediatric patients with cancers. This is a joint presentation -- as you've mentioned, I'm together with my colleague, Dr. Kholmanskikh -- and has been compiled together with colleagues from the European Regulatory Network.

This is our usual disclaimer. This is the overview of our talk. We'll provide general reflections on dosage selection and optimization, including pediatric specificities, followed by some examples; examples which are reflective of the current approach taken by the EMA, the Paediatric Committee, PDCO, at this stage of redevelopment discussions during the pediatric investigation and assessment, PIP assessment, governed by the EU pediatric regulation. I will then hand over to my colleague for examples at the time of marketing

authorization and along the product's lifecycle. Finally, key considerations and some references to your guidance will be highlighted.

We would like to start with general reflections on pediatric development to emphasize, really, the importance of ensuring that appropriate dosage selection and optimization since early initial study design discussions are taking place such that all available evidence -- and we've heard that today already -- including quality, preclinical, and clinical data supported by relevant methodologies, are taken into consideration to support the identification of an optimal dosage early. Because pediatric oncology drug development targets rare diseases, it's paramount in children to maximize robust evidence generation such that it supports the necessary decision steps along the lifecycle management.

We would like to stress as well that non-availability, or non-relevant, of existing adult data is not a reason to delay planning and initiation of pediatric development. Appropriate

design considerations for pediatric development authorized to optimal dosage are, of course, context-dependent. We've heard lots already today that it depends on the product, cytotoxic product or molecularly targeted agent, and what is the target population. Is it a combination development and is there relevant evidence available to be utilized to inform pediatric trial designs?

This schematic overview visualizes the context dependency related to the dose exposure-response relationship, appreciating the interdependencies, as outlined on that slide, between the drug under evaluation and the population treated. It's important to ensuring a sound understanding of the PK/PD, or exposure-response relationships, and the relevant pediatric target population, and also to support potential similarity on exposure-response relationship to the relevant biomarker-positive patients across age groups to contribute to potentially leveraging relevant prior information. I'm referring here to the use of extrapolation. We

will come back to this visual overview later in the presentation.

Safety and pharmacokinetic characterization on the individual product remains the key objective for initial exploratory trials. There is the acknowledgement that indeed the classical approach identifying a maximum tolerated dose does not take into consideration specificities; for example, continuously [indiscernible] and over-targeted [indiscernible] therapies, which may elicit clinically relevant activity already at lower doses and later onset toxicities beyond the first one or two cycles of therapy. Taking these considerations into account, early and continuous regulatory support to timely determine optimized dosage, including effects on biomarkers and outcomes, is paramount.

For pediatric drug development, a PIP life cycle approach is applied to support development efforts on a continuous basis and adequately early data generation to inform subsequent development design considerations when moving forward into a

[indiscernible] or registrational development, and regulatory support through the PIP enables ensuring continuous discussions to identify optimal dosage based on data in close collaboration with all stakeholders.

When it comes to pediatric dose selection and optimization, as mentioned earlier, developers should justify proposed dosing regimens, including potential combination developments in the context of existing nonclinical or clinical data as relevant in support of a development in the intended target population, which would include all relevant age subsets. If a pediatric stand-alone development is foreseen with some prior data in adults, lacking or not being relevant, general guideline considerations apply, and that might require also evaluation of alternative dosing regimens.

With regard to starting dosage considerations for pediatric trials, the pediatric committee is commonly agreeing to apply allometric scaling based on body weight or body surface area

using exposure matching, taking into consideration allometric scaling, as well as maturation considerations. But we also see, although less often, pediatric dose escalation designs using, for example, 80 percent of the recommended phase 2 dose as starting dose. The latter approach can be based on potential safety concerns identified in adults.

Our overarching objective remains facilitating identification of an optimal dosage regimen early, whilst acknowledging that evidence generation to supporting further dose optimization may have to be seen as part of a product's lifecycle management such that the totality of evidence might be available only at a later stage. We're, hence, also considering within patient dose de-escalation and titration as appropriate when sound, adequately justified, and predefined.

On the next two slides, we would like to give you some examples of discussions we've had with developers and sponsors during discussions related to dosage selection and optimization. The common theme, which you require, is further

justification related to the adequacy of the chosen dosage approach in the context of existing usually adult data, particularly body surface area and body weight-based dosing, accounting for variability in exposure levels, often characterized through and in support by modeling simulation from adult data and using relevant predefined cutoffs, either age or weight.

Finally, further discussions occur on how modeling and simulation models account for ontogeny maturation considerations for the entire age range proposed for development within the PIP, and usually rate to the lower weight or age [indiscernible] cutoff on the discussions.

Having in mind the intended target population, we also request, as relevant, discussions related to potential drug-drug interactions and how those could potentially impact achieving a relevant target exposure, particularly since different combination developments may be envisaged as compared to adults. We have had cases where, indeed, drug-drug interactions related to

pediatric specific backbone therapies used for a combination led to increased toxicities, limiting achievement of the matched target exposure. Drug-drug interactions can often be extrapolated from adults; however, in younger children where, for example, the liver is not fully developed, extrapolation of drug-drug interactions may become more difficult, depending on the individual medicine or product.

Other considerations are related to evaluating target engagement, target occupancy, including early assessment of biomarkers, all to support early evidence generation, including signals of activity using an optimal dosage to inform go-/no-go decisions to move forward into a pivotal or registrational development. We're also seeing increased use and are supportive of novel designs for dose finding such as model-based and model-assisted designs.

On my last slide, before handing over to my colleague, I would like to emphasize that depending on the available knowledge and the respective

context when discussing pediatric development as part of a PIP assessment, we are commonly challenging developers and how the totality of data are planned to be generated in an early-phase trial is intended to inform appropriate dose finding and dosage optimization, particularly in cases of expected longer term use. This includes -- and we have not mentioned that yet in our reflections -- the use of patient-reported outcomes. This is to ensure that when a PIP is agreed, we're all clear on what data are needed to inform identification of an optimal dosage and how the totality of evidence can then be used by progressively moving forward.

This is facilitated by using PIPs as a living document, if you wish, providing continuous regulatory support for evidence and duration based on relevant data as the development progresses.

With that, I would like to hand over to my colleague.

Guest Speaker Presentation - Olga Kholmanskikh

DR. KHOLMANSKIKH: Thank you. Olga

Kholmanskikh, clinical assistant at the Belgium Federal Agency for Medicines and Health Products, member of the Oncology Working Party, and alternate at the Committee of Advanced Therapies at the EMA.

The second part of the talk is dealing with current approach and practical considerations for potential dosage optimization as assessed at the time of marketing authorization, but also along the lifecycle of medicinal products. The factors, with potential impact on pharmacokinetics and/or pharmacodynamic variability, can be particular phenotypic characteristics such as weight and phenotypic translation of some genotype, such as those for metabolized enzymes and their age-related antigen. Other phenotypic characteristics of potential relevance -- for example, for immune oncology medicines -- in order to understand the ontogeny of physiological processes, could be qualitative or quantitative features of immune cells.

As regard to more characteristics, the genotypic makeup of pediatric tumors can be

substantially different from that of adult cancers and manifest distinct prototypic characteristics. These and many other factors, such as concomitant exposure to other medicinal products, are to be taken into account for dosage optimizations in pediatric patients with cancer, while defining the main sources of variability and translating this into dosage recommendations.

Importantly, biomarkers can serve different purposes during the dosage optimization process, from determining sources of intra- and inter-patient variability to defining more homogeneous targeted patient populations selected by a biomarker. The context dependency of dosage optimization in terms of extent of development in adult patients and maturity of dose exposure-response relationships has been emphasized by my colleague.

The case samples that are presented on the next slides will only help to illustrate some elements of approaches taken for specific medicinal products at the time of marketing authorization for

dosage selection and optimization, including postmarketing measures to address uncertainties.

This case example concerns one of asparaginase formulations used within combination regimens in pediatric and young adult patients with acute lymphoblastic leukemia. The non-human origin and the immunogenic characteristics of pegaspargase, also due to PEG molecule and the linker, can result in development of specific anti-drug antibodies and hypersensitivity reactions with inactivation of the drug in case of neutralizing potential of such antibodies. Therefore, treatment may be monitored by measuring the drug activity necessary to asparagine depletion, according to its mechanism of action.

Dose adjustments at suboptimal levels are possible, as well as switch to another asparaginase in case of silent inactivation. Investigation of potential sources of high inter-patient variability beyond body surface area described could lead to further dosage optimization. Notably, pharmacodynamic activity was assessed in pediatric

patients through several measurements of asparaginase in sera and cerebrospinal fluid during the development.

In this second example, for small molecule kinase inhibitor, selumetinib, approved in pediatric patients with neurofibromatosis type 1, age 3 years and above, BSA-based dosing is also used with [indiscernible] and function of available strengths of capsules. BSA was shown to have impact on pharmacokinetics in the population pharmacokinetic model. Notably, one of the initially agreed pediatric investigational planned studies was subsequently used as a postmarketing measure to evaluate pharmacokinetics of the age-appropriate formulation in younger pediatric patients and tolerability, especially at longer term.

Biomarkers played a determinant role in simultaneous development and approval in adult and pediatric patients of another small molecule kinase inhibitor, larotrectinib, approved regardless of the tumor type. It's dosing is also based on BSA

with a defined maximum amount per dose. Population pharmacokinetic analysis showed age-dependent differences in systemic exposure, which is high in younger patients. Associated uncertainties led to a postmarketing commitment to collect more pharmacokinetic data and to revise the dosing recommendations, if needed.

Rule-based 3-plus-3 design considering toxicity and defining maximum tolerated dose was used for a dose-finding study of selpercatinib in adult patients. While other types of data were also considered, clear exposure-response relationship could not be shown at the time of the marketing authorization assessment.

Population pharmacokinetic analysis determined dose and body weight as significant covariates for pharmacokinetic variability, resulting in cutoff of 50 kilograms for flat dosing. It was developed in adolescents and adult patients, considering the similarity of the disease molecule of thyroid cancer and targeted to biomarker-defined population. The ontogeny of

metabolized enzyme was allowed [indiscernible] to consider adolescents as similar to adults in this case.

The next three slides provide examples of developments based on monoclonal antibodies primarily to target antigens on the surface of tumor cells, and in case of this specific [indiscernible] engages on the surface of immune cells. One of the earliest developments with recent approval in pediatric lymphoma patients from the age of 6 months is rituximab. It is administered at the same BSA-based dosing as in adults.

BSA had an impact on clearance and foreign parameters similar to other monoclonal antibodies. In this case, and considering the age range, previously developed population PK model was updated to include a maturation factor to the constant clearance component to account for the potential effect of the neonatal Fc receptor variation with age and supported an extension to the age group from 6 months to 3 years, despite the

lack of clinical PK data.

For a second example of bispecific T-cell engager, blinatumomab, step-up dosing is used also in pediatric patients aged 1 year or older with refractory or relapsed acute lymphoblastic leukemia to mitigate the risk of cytokine release syndrome. In both indications, by line of therapy, [indiscernible] stratifies patients with high body weight for a fixed dose, while patients with lower weight are dosed based on BSA, which was shown to influence the PK in PopPK model.

The third example is a fixed-dose combination of two monoclonal antibodies, nivolumab and relatlimab, indicated in adolescents and adult patients with melanoma. The flat dosing for each antibody is established for adolescent patients weighing at least 30 kilograms. Clearance and volume of distribution in adolescents relative to adults were estimated for nivolumab. With respect to relatlimab, no adolescent PK data were available, and PopPK simulations were performed. In this situation of comparable pathophysiology

between age subsets, efficacy and safety data can be extrapolated based on comparable exposure. The infusion duration was shorter based on predicted systemic exposures.

This was examples of only some aspects related to dosage optimization, while it is acknowledged that other aspects are also to be considered when elucidating clinical pharmacology of monoclonal antibody-based medicines schematically presented here. These are also relevant for more complex examples: disease-specific antibodies, antibody drug conjugates, and so forth.

Among the factors with potential impacts on pharmacokinetics or pharmacodynamics in pediatric patients are the previously mentioned. In one example of variability is the neonatal Fc receptor expression, potential differences in target-mediated drug disposition; and immunological mechanisms, just to cite some. For establishing dose exposure-response relationships, this and other factors need to be considered in a time-wise

manner as long as a potential impact to changes in baseline patient and disease characteristics would occur.

Establishment of reliable dose exposure-response relationships is essential for dosage selection and optimization, extrapolation, and informing study designs, including optimal sampling. It is well acknowledged that there will be a degree of uncertainty in those exposure relationships in pediatric patients of concern; however, maximally leveraging the prior knowledge is applicable, considering pediatric specifics [indiscernible]; and applying pharmacometrics and other relevant approaches, sequentially or in combination, are clear additional opportunities to ensure optimized dosage for pediatric patients with cancer.

In conclusion, on key considerations, context is essential, as well as ensuring that all relevant evidence is used to inform early dosage finding. Non-availability or limited applicability of adult data is not an argument to delay pediatric

developments, in general, and timely dosage and overall benefit-risk optimization. It is key to ensure maximized data generation while ensuring novel methodological approaches, confirming the simulated dosages, and considering more expanded inclusion of the patient voice in the totality of data.

Early and continuous interactions with regulators is key, supported through the evolutionary, step-wise pediatric investigation plan framework and use of mechanisms in place for close collaboration between EMA and FDA.

Here is a selection of references provided for further reading. We would like to acknowledge colleagues in the European Regulatory Network that contributed to this presentation. This is the end of our presentation. Clarifying questions are welcomed later on, and now I am pleased to hand over to our next speaker, Dr. Elizabeth Fox. Thank you.

Guest Speaker Presentation - Elizabeth Fox

DR. FOX: Good day, everyone, and thank you.

I'm Beth Fox, a pediatric oncologist at St. Jude Children's Research Hospital. Thank you for the opportunity to discuss the academic perspective on dose and dose optimization for children with cancer and drug development. I have nothing to disclose, but I will discuss some off-label uses. This presentation reflects my opinion based on the referenced data available in the public domain, and does not reflect the opinions of the institutions, sponsors, cooperative groups or consortia with whom I am affiliated.

I think we all agree that the unifying goal of childhood cancer drug development is to improve cure rates, and in the first panel, you can see that we all know that the 5-year overall survival for children with cancer has increased dramatically since the 1960s and is currently over 86 percent.

We also have a need to diminish acute toxicity. The middle panel is actually data from a cooperative group -- rhabdomyosarcoma -- study in newly diagnosed patients, and it states that about 75 percent of our patients tolerate

life-threatening or grade 4 toxicities during the course of curative therapy. We would like to diminish that acute toxicity, and very important as we've heard today, eliminate delayed effects.

This is a graph from the Childhood Cancer Survivorship study that was published by Dr. Armstrong that looks at the cumulative incidence of grade 3 to 5 chronic health conditions in survivors in blue compared to their siblings in gold. As you can see, by age 40, survivors of childhood cancer have a 40 percent incidence of a grade 3 to 5 chronic health condition.

As we know, each year in the United States, there are nearly 16,000 children diagnosed with cancer. The table here demonstrates the most common childhood cancers, as well as the common age of diagnosis, and this is a very important consideration as we consider developing new drugs for these children.

For example, acute lymphoblastic leukemia is the most prevalent, with 20 percent of our diagnoses each year in the United States, and this

most commonly occurs at the age range of less than 8 years. Brain tumors and CNS tumors, because they have so many different histologies and account for 18 percent of the children diagnosed with cancer each year, they occur over a very broad age range throughout pediatrics, from 0 to 19 years. And to point out neuroblastoma in the middle of the chart, with about 5 percent of our children with cancer being diagnosed each year, these occur in very young children, less than the age of four. These are important considerations as we consider not only the rarity of childhood cancer, but the populations at which they are diagnosed.

The objectives of my talk today are to illustrate why rational dose determination is a prerequisite for optimization in drug development for infants, children, and adolescents with cancer, and I would like to do this by showing some examples of dosing methods for children, dose determination, and the impact of formulations.

As we've heard this morning, the ontogeny of childhood development impacts drug dosing in

children. We know that there is a dramatic weight change. There's a 10-fold increase in weight from birth to 10 years, from about 3 and a half kilograms to 32 kilograms. In addition, there is at least a 2-fold increase from age 10 years to adulthood if you consider 32 kilograms to 70 kilos and above. We know that weight is not literally related to body surface area as we consider how to dose children. Excretory organ growth rate is proportional to body weight, and the greatest changes in renal and hepatic function occur during the first year of life.

Aspects of normal growth and development may be inhibited by targeted anti-cancer agents, and this is one of the things that we really consider as we consider eliminating late effects. We cannot measure late effects until we have survivors of childhood cancer who have been treated with targeted agents.

On this next slide, this really follows what Dr. Karres was discussing in terms of comparison of dosing methods, but I'll do this with a specific

example of a monoclonal antibody with an adult recommended dose of 600 milligrams. I'll look at each of the types of methods we use for basing our doses, and I'm going to apply this to three children in the far-right of the table, a 5 year old, a 6 year old, and a 12 year old.

For weight-based dosing, or milligram-per-kilogram dosing, this is a continuous variable, it's patient-specific, and it's easily measured. The disadvantages of this method is we often debate whether we should use actual versus ideal weight and the impact of concomitant medications such as dexamethasone on the weight of a child. Weight also fluctuates. Particularly in our smallest children, it can fluctuate day to day, week to week. Most importantly, when we use weight-based dosing, the constraints of oral formulations are predominant and, importantly, milligram-per-kilogram dosing is a systematic dose reduction in infants, and the next slide will go into that.

As you can see with weight-based dosing,

based on this monoclonal antibody with an adult dose of 600 milligrams IV, these are the doses that would be administered to the three example patients. I want to compare that to what happens if you use body surface area dosing or milligrams per meter squared. This is, as well, a continuous variable, it's patient-specific, and I think it's really important that this is also in a limited range. Body surface area in the smallest of children is 0.23 meters squared, and goes up to maybe a maximum of 2.5 meter squared in the largest adult, and that is primarily because height is the driver of body surface area.

Some disadvantages of this method are that it does include calculations, and there are multiple formulas to do it. In addition, similar to weight-based dosing, there are constraints with oral formulation, but I'd like you to take a moment to compare what happens with the meter squared dosing compared to the per kilo dosing for each of the example patients.

Finally, we've heard a little bit about

age-based dosing. Age, as you know, is a categorical variable, and it's very easily measured. It's why acetaminophen is based on age with the dosing so that parents can dose it in the outpatient setting. However, age changes, as you know, with your birthday, not with your physiology or your ontogeny, and please look carefully at how the doses in the 5 year old and 6 year old changed dramatically, perhaps on your birthday, just because of a day of the year on the calendar.

Finally, we heard a little bit about fixed dosing, which is very convenient in adults, but it doesn't account for this 10-fold weight change in childhood, and as you can see is the least specific for children. When we develop a drug, we think first about the first step being this dosing method, and we have to consider this and its impact on optimization for the individual patient.

On the next slide, I'll show you some of the dosing strategies that are used by the Children's Oncology Group. First, we've spent a long time developing dosing tables for many of our standard

cytotoxic drugs. The goals of this project were to eliminate a quantum leap; that is, age or weight-based thresholds for the transition from the weight-based to the BSA-based dosing methods. What we found was that over phase 2 and phase 3 COG trials, there were more than 11 different thresholds placed that included both age, weight, and body surface area in these transitions, and they were very different between different trials.

We also wanted to gradually reduce the systemic dose reduction that is created by milligrams per kilogram. So in the graph shown for vincristine, I'll tell you what I mean. We have access to data from 1500 children with Wilms tumor, and we calculated their dose of the cytotoxic, in this case vincristine, on the milligram-per-kilogram dosing plan. That's the upper line. We then used those same children and calculated what their standard milligram-per-kilogram dose would be. That's the lower line. So when I say there's a systematic dose reduction between these two methods, that's precisely what

I'm talking about, and that is an intentional dose reduction because, as you may know, for cytotoxic drugs, we've long preferred milligram-per-kilogram dosing because of the toxicity we saw with cytotoxic agents in the smallest children.

To develop the BSA-based table that you see on the slide, what we did was we used linear regression to determine the doses that would be delivered, from a 0.2 meter squared child to a 0.6 meter squared child who were approximately 3 years of age, and we modeled those doses. The dotted lines you see there are actually the most important drivers of what those doses in the table are, and it's the administered dose based on the measurable volume of vincristine that you can pull up into a syringe to deliver to a baby. So we've developed these tables for many of the cytotoxic drugs that we use, and we are currently validating them with some PK studies.

The other strategies that we use are the use of dosing nomograms for oral agents that are standardized by body surface area bands, and this

permits adequate dose reductions, if necessary. It also ensures that our dose levels in a dose escalation trial are discrete. And finally, within the COG, we generally study unlimited number of dose levels for dose exploration.

We acknowledge the importance of pharmacokinetics and pharmacokinetic modeling. It's critical to understanding pediatric dose and the tolerability of response. Extrapolation from adult data, however, often neglects the dramatic weight change during childhood, and I think this is an area of caution if we were to only extrapolate our doses based on adult data. Inclusion of detailed pharmacokinetics from limited dose escalation trials in children could validate the assumptions of an extrapolated PK model.

Finally, categorical dosing methods will increase the variability in exposure in children. Determining a plateau of a dose response or dose exposure curve, which we've heard a lot about this morning, or thresholds to require these things, these require responses. And to Dr. Glade Bender's

earlier question, when we do phase 2 trials, we often have very small trials of 20 patients and see 3 to 4 responses. So when we do these types of modeling based on response, the first criteria is how many responses do we have.

On the next slide, I'd like to take you through a current example. This is the trial that was recently published by Dr. Bouffet. The goal of this trial was to determine a monotherapy dose of the MEK inhibitor trametinib and seamlessly and rapidly move to a combination of trametinib and dabrafenib.

The graph here, I will use to describe the trial. It was dose escalation originally from 0.125 milligrams per kilogram per day of trametinib to 0.25, and the other planned dose was 0.04 milligrams per kilogram. You can see, based on this graph, that the average concentration of trametinib was measured by age group, and you can see that at the 0.125 lowest dose level, nobody achieved the target exposure in adults, which was 12 nanograms per mL. In addition, you can see at

0.04, not only did we see toxicity, we saw increases in this average concentration. There was, however, at the 0.25, the youngest of patients were right on the border of whether they were above the target concentration; therefore, the study was amended and a 0.023 milligram-per-kilogram dose was added for the youngest patients.

What came out of this study was an age-based dose recommendation for less than 2 year olds receiving a higher milligram-per-kilogram dose compared to children 2 to 17 years old, who got 0.25 milligrams per kilogram, and young adults greater than 18 received the adult recommended dose of 2 milligrams.

What was critically important to the conduct of this study was the oral liquid formulation of two available tablet sizes. But when we look carefully at the pharmacokinetics, there's actually no difference between the average concentration at the 0.025 milligram per kilogram or 0.023 milligram-per-kilogram doses levels, and you can compare that to the model data in adults that

included patients as young as 19 years of age.

So you may ask, is age-based dosing necessary if we base according to size? On the next slide is what the FDA actually published as the label for trametinib dosing, and clearly the FDA heard the question, is age-based dosing necessary? So on the next slide you can see the actual FDA label, and you can see that they have prescribed this drug, trametinib, according to body weight, and included separate tables for the oral solution and the tablets.

Importantly, if you look at the 6 to 37 kilogram body weight tablet recommendation of 1 milligram, and you compare it to the oral liquid formulation in those dosing, you can see that there's really only a 10 to 15 percent dose excursion among the patients who got the oral liquid compared to those who get the tablet.

On the next slide, I'll expand a little bit on what Dr. Wessel was talking about for crizotinib. This is the phase 1/2 trial of crizotinib that was conducted by the Pediatric

Early Phase Clinical Trial Network and the Children's Oncology Group. As we know, crizotinib is an oral inhibitor of the anaplastic lymphoma kinase. In adults, it's approved at a 250-milligram BID dose or 45 milligrams per meter squared twice daily. We know that this drug is now FDA approved at the recommended dose in children of 280 milligrams per meter squared.

So how did we get there? We got there, in part, because of the preclinical evaluation of crizotinib in neuroblastoma, which clearly demonstrated that for certain mutations in ALK that occurred in neuroblastoma, we were going to require higher exposures to crizotinib in order to inhibit ALK; and therefore, we conducted the phase 1 trial in the middle panel.

Initially, this trial was based on four dose levels, from 100 to 215 milligrams per meter squared per dose, and we were able to achieve that without exceeding the maximum tolerated dose. Because of concerns that we were not achieving a high enough concentration in patients with

neuroblastoma, we proceeded with two additional dose levels, and ultimately exceeded the maximum tolerated dose and determined the MTD at 280 milligrams per meter squared per dose twice daily.

This very large phase 1/2 study offered the opportunity to look at pharmacokinetics in a large number of patients, as well as four separate formulations. As you can see by this graph, which is dose-normalized exposure, or AUC, as a function of age, there really isn't any discernible difference in the different formulations or according to age; however, there is a lot of variability.

In the next slide is the outcome and responses that were seen in this study. I'm actually going to start with the swimmers curve with the pink lines for neuroblastoma. Crizotinib is an active agent in a subset of 1275 ALK mutated neuroblastoma at the top of that curve; however, it had no activity in patients with neuroblastoma harboring other hotspot ALK mutations or

amplifications.

Moving to the left of the slide are the swimmers plots for acute anaplastic large-cell lymphoma at 165 milligrams per meter squared or 280 milligrams per meter squared BID. You can see that there are responses at both of those dose levels, and we know that in patients with inflammatory myofibroblastic tumor, toxicity and response were similar across the dose range.

To the question that was posed about is optimization of crizotinib's FDA approved dose necessary in children with ALCL or IMT, we agree that it is, and there has been a completed phase 2 study in patients with ALCL, where crizotinib was combined with a backbone cytotoxic regimen, and we used a 165 milligrams-per-meter-squared crizotinib dose to do that.

So I think this example and this study demonstrate that target exposure is target dependent, and we need a better characterization of what the targets are in pediatric cancers and do they require the same exposures to be inhibited.

We've talked a lot today about pediatric appropriate formulations, and on the next slide we know that this includes bioavailability; and relative bioavailability; taste; palatability; the concentration or volume that the child would have to take; stability; the preparation; and the administration are all features of what an appropriate pediatric formulation should include. The graph is a study that was completed by Dr. Chuk that looks at cabozantinib and looks at the exposure of cabozantinib across this phase 1 study that had three planned dose levels, 30, 40 and 55 milligrams per meter squared.

When we looked at the PK data for this, we realize, you see, there is no difference in those dose levels in the actual exposures in patients, and we looked at the average daily dose administered to the patients who had PK, and you can see that there is very little difference in the average daily dose. So when we plan dose escalation trials, formulation can constrain us to what we can actually do, and that impacts the

exposures. What's important about this trial is that it did not define a maximum tolerated dose because the MTD was not achieved; however, we did declare a recommended dose, based on, as Dr. Wessel indicated, we used the toxicity across all of the cycles that the children received to determine what the recommended dose was.

So the most important factor in dose optimization is an appropriate formulation, and that's demonstrated on the next slide with larotrectinib and entrectinib. These are two NTRK inhibitors, and we've heard about them already today, so I won't go into detail. But as we know, the larotrectinib study was biomarker enriched and selected, and did not seek a maximum tolerated dose, and ultimately determined the dose of 100 milligrams per meter squared twice daily with a maximum of the adult dose 100 milligrams BID in children. Responses were seen, and most importantly, these studies were conducted from the very first study to include an oral solution, and this ultimately resulted in FDA approval in 2018

that was both age and histology agnostic.

In comparison, entrectinib, another NTRK RAS inhibitor, was published by Dr. Desai in 2022. This was designed very differently. It was designed as an MTD study and did indeed push to the MTD 550 milligrams per meter squared, which is much higher than the adult recommended dose. Part of the reason for doing this was because of the capsule formulation restrictions, and ultimately, entrectinib was FDA approved in 2019 for children greater than or equal to 12 years of age with the dosing seen here.

On the next slide, I'll summarize by saying that maximum tolerated dose is not an appropriate endpoint for many targeted agents; however, variability and formulation impact the utility of pharmacokinetics as an endpoint. Pharmacokinetics and age-related toxicity data are essential throughout the drug development timelines, and accurate dosing across the age spectrum, limited dose exploration, and detailed pharmacology are needed for pharmacokinetic modeling in children.

In my opinion, dose optimization in children requires drug-specific considerations, including formulation, pharmacokinetics, variability, and target exposure in pediatric cancer. Optimization of doses in children requires defining the dose-response relationship, not randomization of doses. Clinical trials in children cannot wait for optimized dosing in adults, and I was really thrilled to hear the presentations by the FDA that supported that position.

On my last slide, I'll just remind us that there's only a quantitative difference between a drug and a poison, and this is a slide that I've used since I ran my very first trial way back in the '90s of arsenic trioxide. So with that, thank you very much, and I will like to ask Dr. Samuel Blackman to present his slides and presentation.

Guest Speaker Presentation - Samuel Blackman

DR. BLACKMAN: Thank you, Dr. Fox, and thank you to the organizers of the meeting of this subcommittee for inviting me to share some thoughts. My name is Sam Blackman. I'm a

pediatric oncologist and co-founder, and head of Research and Development at Day One Biopharmaceuticals.

I'd like to provide the perspective of a pediatric oncologist and drug developer working in the biopharmaceutical industry, and my goal here today is to provide a perspective of some of the forces that govern our approach to drug development problems within biopharmaceuticals, and some of the challenges that we're encountering. And in doing so, I hope to offer perspective and some ideas to help us all work efficiently together towards the common goal of ensuring that we treat pediatric patients with the right drug at the right dose.

Again, on my disclaimer here, I am speaking as an individual, and my comments here reflect my personal perspective on this topic, and the publicly available data that I cite do not, in any way shape or form, represent the views of Day One Biopharmaceuticals. I also want to acknowledge the fact that I'm not speaking on behalf of the entire biopharmaceutical industry, but rather as an

individual working in the industry. My remarks are not meant to represent every possible perspective.

It's ironic that while cancer therapeutic development really started, in earnest, in the late 1940s and that combination development, also starting in the late 1940s and early 1950s, really started with pediatric oncology, that there remains a significant gap between the start of clinical trials in adults and the start of clinical trials in children, and this is, of course, reflected in the gap between the approval of new therapies for adults and new therapies for children. And this is despite the incentives and regulatory requirements in both the United States and Europe, and the pace of oncology drug development continues to lag despite those incentives.

Not surprisingly, there are a lot of causative factors here. Some of these are structural within the ecosystem of drug development; some of them are cultural within the drug development ecosystem. And while there have been an increasing number of motivating forces over

the years to promote pediatric drug development, they are often counteracted by opposing forces that generate friction in the system.

I want to note that none of these are a lack of desire to see new therapies brought forward for children -- I think we all agree that this is a shared goal -- but within industry, there are forces that shape the way that work is prioritized. On the side of forces that motivate the development of new therapeutics for children, of course there are regulatory requirements such as pediatric investigation plans and the RACE for Children Act that require initial pediatric study plans.

There are, of course, internal champions within industry and the advocacy community; improvements in trial design; advances in modeling and simulation; various regulatory incentives that are offered; and, of course, the broad moral and social imperative to make sure that we have new therapies for children developed at the same pace that we do for adults.

But of course on the frictional side are, of

course, cost; lack of resources in terms of adequate preclinical models; a tendency towards risk aversion within the biopharmaceutical industry; within smaller companies, intense capital demands; on the technical side, oftentimes insufficient target validation early on in pediatric diseases; a lag in terms of the initiation of pediatric formulation development; and of course, and I think most importantly, a limited number of patients and the need to evaluate patients across age ranges, which is something that's been cited here.

I also want to highlight a couple of other factors, including a herd effect within the biopharmaceutical industry, limited system capacity and, of course, the need for combination therapy in many indications. So I'd like to dive into a few of these topics a little more deeply.

Here on slide 5, I want to highlight the fact that the landscape for innovation within the biopharmaceutical industry has shifted more towards smaller companies. A recent report from Bio shows

that 65 percent of new drugs approved so far in 2023 have come from small companies, but as you can note here in the paragraph above, we're also witnessing the cyclical nature of biotech investing, and many small companies are limited in their ability to access capital, either public or private, to advance their pipelines. As a result, pipelines are being thinned, and development programs are often times focused on the work that creates the value necessary to allow them to raise funds to continue their efforts and ensure sustainable businesses.

The second challenge that we face within the biopharmaceutical industry results from our having picked a lot of the low-hanging fruit. Many of the druggable oncogenic kinases have already been drugged, and the easier biological targets for antibody drug conjugates, or monoclonal antibodies, or cell therapies, have been addressed. As we've moved on to harder biological problems or have pursued novel chemical approaches such as targeted protein degraders; ADCs for new cell surface

targets; computationally assisted identification of [indiscernible] pockets on previous and druggable proteins, all of these are riskier areas of drug development, and as everyone knows, the failure rates in drug development are high.

What we're seeing here, particularly in the upper left-hand corner, is a reversal of the trend that we saw in the first half of the 2010s, where the success rates for oncology drug development, from phase 1 through new drug application submission, went from less than 10 percent to over 20 percent around 2016. As you can see, we've now seen success rates drop, and we're seeing early-phase and late-phase failure rates increase.

Another challenge, particularly for pediatric oncology and for small companies, is the herd effect that we've seen over the past 10 years, where the number of assets for a given drug target has skyrocketed. As a result, targets that are relevant to pediatric oncology indications, many of which in this era of precision medicine are subsets of already small disease populations, will have

multiple agents that require testing in pediatric populations.

As noted on the Y-axis here, the two major pieces of legislation that added requirements for pediatric development pre-dated this inflection point, and despite the efforts of cross-stakeholder discussions, such as the accelerated pediatric strategy forums, prioritization remains a challenge for the pediatric oncology ecosystem. As the trial-eligible population becomes smaller, the time that it takes to accrue patients increases, especially given competition with cooperative group trials and investigator-sponsored research.

While it may be unusual to talk about the cost of clinical development, given that the majority of new molecules are being developed by smaller biotech companies, I believe that it is relevant to discuss the development cost for industry, particularly in an environment where investment capital may be constrained. In talking to my colleagues in the pediatric oncology field outside of industry, many are surprised by the high

cost and number of cost drivers for industry-sponsored research.

Current per patient trial costs are typically budgeted in the $200[000] to $250,000 per patient range and are driven by a variety of factors. Especially for small companies, given the high cost and competing priorities required to achieve sustainability, there is often times a business need to defer investment in pediatric drug development until there's a high confidence that the lead indication has a path to proof of concept or registration, as these are often the catalysts that allow for capital formation and sustainability of drug development efforts.

I highlight here some of the unseen costs within drug development, including and beyond internal resources, the dependence on contract research organizations for clinical trials conduct and imaging assessment; data management; ongoing pharmacovigilance; individual site costs; and external lab costs, as well as formulation development.

I also believe that it's relevant to indicate that the broader landscape for industry-sponsored drug development continues to evolve as the country grapples with the best way to address the cost of prescription drugs. The recently passed Inflation Reduction Act has shifted the exclusivity period for small molecules, and in doing so, appears to disincentivize small molecule development.

Small molecule medicines are disadvantaged by the law by allowing Medicare to negotiate prices after just 9 years compared with the 13 years afforded to large molecules or biologic treatments. And it's important to note that the vast majority of oncology drug development is really spurred by the pursuit of targets that are relevant to adult indication and, of course, then backing into pediatric development for targets that are relevant to pediatric cancers.

The IRA clock starts running after the first approval, so the strategy of pursuing approval in smaller indications first -- for example, smaller

biomarker-defined subsets -- is potentially disfavored. As such, there may be less of an incentive to pursue a pediatric indication as the lead indication with which to file, even if it's available. For many small biotech companies, limitations to a return on investment for small molecules and rare indications may make it more difficult to raise capital and could shift development focus to larger indications and/or biologics.

On slide 10, I'd like to highlight existing challenges in determining the best time for companies to start investing in pediatric dose confirmation and dose optimization studies. This very simple schema attempts to highlight some of the questions that are asked internally as programs move forward in development for adults. Proof of concept, oftentimes the catalyst for further investment internally, is not a fixed milestone. Depending on the target, the disease, and the endpoint, proof of concept -- which some define as proof that the therapeutic intervention is likely

to convert clinical benefits to patients, and it may include but sometimes goes beyond just changing a surrogate endpoint -- may occur early in phase 1 or may occur late in phase 2, either single-arm or randomized phase 2 studies.

Companies have been historically reticent to start pediatric phase 1 without adult proof of concept despite legislation requesting, if not requiring, pediatric drug development efforts to start the adult at end of phase 1. There is historically a low incentive to invest in pediatric formulation development before adult proof of concept due to a high risk of program failure.

Finally, some of the infrastructure that's needed for pediatric dose optimization may not be fully in place until later in development, such as pediatric-specific pharmacodynamic biomarker development if you're pursuing a different indication than the lead indication in adults; adequate size population PK models; identification of pediatric responder subpopulations; and sufficient anti-tumor activity to enable

exposure-response modeling.

Despite these challenges, as a pediatric oncologist and drug developer, I absolutely agree with the premise outlined by Dr. Donoghue at the start of the meeting. It is essential for us to give the right drug, to the right patient, at the right dose. But as Dr. Fox highlighted in the last talk, dose optimization is important to maximize efficacy and maximize both short-term and long-term safety, and this requires an understanding of the dose-response relationship, as well as the dose toxicity relationship; and some of these relationships are not clear early in development and require larger or longer studies.

I also want to highlight some additional aspects of pediatric oncology drug development that are different compared to adults. Some of the translational models for pediatric cancers are far less abundant, making preclinical dose optimization more of a challenge. Obviously, obtaining samples for pharmacodynamic biomarkers is potentially easier in adults compared to children. Liquid

biopsies may be useful for hematologic malignancies or some solid tumors, but may be insufficient for brain tumors, which is, as was noted at the beginning of Dr. Fox's presentation, the most common solid tumor of childhood.

In addition to broad population recommended for dose optimization studies in adults, it would need to be even broader for pediatric oncology, owing to differences in age and development, and optimizing dose for near-term safety and tolerability in advance of adult cancers makes sense, but safety in children is far more than just near term and requires long-term follow-up.

Then, of course, there's the problem of combinations. Some new therapies developed for children will be adjuncts to combinations with existing chemotherapy backbone, so monotherapy dose optimization early in development may not be the most efficient place to invest the required time and effort.

So I believe that dose optimization for pediatric oncology is not a question of if, and I

think everybody here will agree to that point, but may be one of when. The maximum tolerated dose may or may not be the optimal dose for targeted therapies. And dose optimization is certainly important to maximize efficacy and maximize both short-term and long-term safety, but there are a variety of factors that needed to be taken into account. And I would argue that all of these points argue for an approach to pediatric dose optimization that doesn't see approval as the deadline for these efforts but rather as a milestone or benchmark, especially given the time and cost pressure on drug development and activities.

I'd like to offer on the next few slides some potential solutions for finding an efficient way to pursue dose optimization that meets the needs, obviously, of patients, but all the other stakeholders involved in this industry. On slide 13, I highlight the need to remove the illusion of precision from small cohorts, particularly in the absence of a pharmacodynamic

biomarker or if there isn't sufficient efficacy data upon which to base a choice of the optimal dose.

It is possible to collect far more extensive pediatric PK data over the longer time frame of late-stage pediatric development or lifecycle management, utilizing modeling and simulation, and extrapolation where possible, and also learning from adult PK/PD, PK efficacy, and PK safety relationships. I would ask the question, is randomizing an additional 6 to 12 pediatric patients of various ages or sizes between two dose levels, either pre or post proof of concept, going to lead to an optimal dose if there isn't a reliable pharmacodynamic biomarker or efficacy data upon which to base a choice? And I do believe that extensive collection of pediatric PK data over the longer time frame of pediatric development may be the more efficient and precise approach.

I'll also argue that it is possible to relax time pressure. Postmarketing commitments such as the one employed for crizotinib are taken seriously

by sponsors. Moreover, pediatric oncologists have a long and illustrious history of pursuing dose optimization in combination development. To achieve more rapid development for pediatric populations, it may be necessary to accept that the initial dose optimization is based on near-term safety, while additional work, including optimization for efficacy or long-term safety, may come later post-approval.

If there is a path to approval in a pediatric indication, I think it's worth asking whether or not delaying review of a file for an active drug for pediatric indication, due to lack of pediatric dose optimization at the time of approval, whether or not that's actually going to benefit patients, particularly in indications where patients are harder to find. Can we make optimization a postmarketing commitment linked to confirmatory trials, or to collection and submission of long-term follow-up data, by including PK data?

Finally, I'd like to highlight the benefits

of using existing incentives and a couple of creative ways of collaborating. Can we link dose optimization to pediatric exclusivity through pediatric preclinical study requests and pediatric investigation plans? I believe that Dr. Karres highlighted the inclusion of dose optimizations as part of PIP in some of the examples that were presented.

I believe that we can work together to collect PK and post-approval studies or as part of registries for long-term safety studies. I think it's worth asking whether or not companies can or should fund the transfer of validated PK assays to central locations, such as the NCI and CTEP, to ensure that they are available for long-term PK data collection and dose optimization studies.

Finally, I would argue that, as Dr. Karres reminded us, PIPs are considered living documents because the time course of pediatric development is long, and we learn many new things along the way. When I was constructing this presentation, I asked myself can labeling for pediatric uses be seen in

the same way? And I found a quote from Dr. Pazdur, who noted that a drug label, quote, "is a living document." Many people have the misconception that the history of the drug ends with the approval of the drug. Really, that is just the beginning, we have to keep in mind, and also have a process of updating these labels.

I hope that my remarks have left you with the message that those of us working in pediatric oncology within industry agree that dose optimization is essential for all cancer therapies, especially for children for whom late effects and long-term toxicities remain a major source of lifetime morbidity and mortality.

I hope that my comments indicate that, for me at least, the point for discussion is not a matter of if, but when to require dose optimization. The challenges existing within the drug development ecosystem are significant, and particularly for small companies who have multiple competing demands and challenges beyond the scientific, these needs should be taken into

consideration.

I'd like to close with a quote often attributed to Voltaire, but one that, in fact, he attributes to someone else, and one that I think is always important to bear in mind for the remarkably complex endeavor that is new therapeutic development, "Dit que le mieux est l'ennemi du bien. Our children deserve the best, but let us not sacrifice the good along the way in our quest." Thank you for your attention.

Clarifying Questions

DR. PAPPO: I would like to thank our speakers, Dr. Karres, Dr. Kholmanskikh, Dr. Fox, and Dr. Blackman, for their excellent presentations.

We will now take clarifying questions for the guest speakers. We have about 10 minutes. Please use the raise-hand icon to indicate that you have questions, and remember to lower your hand by clicking the raise-hand 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 specifically to the 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 very 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 to the next panel member.

The first person is Dr. Edward.

DR. KOLB: Thank you, Dr. Pappo. My question is for Dr. Blackman.

I was struck by your talk, and when we consider the threats to drug development in children, I don't put dose optimization at the top. I put the pace of drug development clearly at the top. And as you pointed out, the RACE Act and PIP incentives for companies are an incentive for us to develop drugs early, and then the financial forces of drug regulations are counterforces. I think that was an excellent point. We see that reality play out every day.

None of us are suggesting that optimization isn't optimal, but as you quoted at the end, optimization may be the enemy of good, and sometimes we just need good. Sometimes we just needed a dose to confirm an efficacy signal because there's no point in optimizing the dose of an ineffective therapy. We need a dose to move forward.

So what I see here as a result of these regulations, of Project Optimus especially, if applied aggressively, are unintended consequences that are going to further delay drug development in kids. From the perspective of the small biotech, what do you think are the important metrics we should be looking at along the way to measure those unintended consequences? Thank you.

DR. BLACKMAN: Well, thanks for the question, Dr. Kolb. I think at the end of the day, it's important for me that we continue to monitor the gap in the initiation of clinical development in children relative to the initiation of clinical development in adults. This was highlighted, of

course, by the paper where Dr. DuBois was the senior author, and it's something that I cite very frequently because that median, of course, it's just that, a median. And you saw on that bar graph from his paper, a vast number of programs where there was a gap of a decade or more between the start of pediatric phase 1.

I think for us, a metric of success in pediatric drug development is really closing that gap and trying to get to what, really, the European Medicines Association pointed out, I think, very early in the pediatric rules that they brought forth; that pediatric development should start as soon as possible at the end of adult development.

I firmly believe that that is something that we all need to adhere to, but I think in instances where you do see an efficacy signal and you do have the potential to move something forward at pace and close the gap between approval that exists between adults and pediatric patients, we should try to take advantage of that and build in commitments to allow for additional work for optimization later,

particularly as it pertains to long-term toxicity. But for me, closing that gap between first-in-adult and first-in-children is, really, probably "the" most important metric.

DR. KOLB: Thank you.

DR. PAPPO: Just a reminder to briefly state your name for the record when you're asking a question and also to turn off your camera if you're currently not asking a question.

The next question goes to Dr. Steve DuBois.

DR. DuBOIS: Steve DuBois, Dana-Farber/ Boston Children's. I have a question for Dr. Fox. I really appreciate you highlighting the formulation issue, which is a rather nuanced issue in terms of we think of formulation as a kid-friendly formulation for children who can't swallow pills, but it really goes a little bit deeper than that even, in terms of how finely we can dose tablet or capsule forms for children who can swallow pills. And as you're well aware, a number of our pediatric early-phase clinical trials have a dosing nomogram that calls for maybe 2 pills

on Monday, Wednesday, Friday and one pill on the rest of the week.

I always worry that if we do PK on that day where they're taking the higher dose, we're sort of overestimating, and if we're doing PK on the day where they're only taking one pill, we're sort of underestimating their PK exposure. So I wonder if you have thoughts or suggestions on how to deal with that, aside from having ways to more precisely dose our young patients.

DR. FOX: I agree that formulation, obviously from my talk, is one of the things I think about a great deal, and your point about when we do pharmacokinetics actually links to what Dr. Blackman was talking about regarding continuing pharmacokinetic evaluation throughout many of the different trials that we may do.

One of the efforts that we try to do in many trials, particularly orally administered drugs with long half-lives, is to abandon first-dose PK and do steady-state pharmacokinetics, where we're likely to be able to collect over the dosing interval six

or so samples and get a very good estimate of what the exposure is at steady state. From an individual patient perspective, that's what really matters, is can we achieve that exposure?

I think your point is very well taken in that that consideration can't be done after we collect all the samples, and these are very precious samples. So I do think we need to be very careful as we consider when we do the sampling, how much sampling, and what is it going to reflect, because at this time, we fully recognize that oral liquid formulations that are palatable would be lovely because we can get precise dosing. We also understand the amount of investment that takes, and to Dr. Blackman's point, in a small biotech, that may not be feasible. And quite reasonably, if we don't know a drug can move forward, that investment may not be wisely placed. Thank you.

DR. DuBOIS: Thank you, Dr. Fox. Nothing further for me.

DR. PAPPO: I have a quick question for Dr. Fox also. I liked your slide very much about

also looking at the context of the disease and how we decide what is the optimal dose. For example, with neuroblastoma versus the IMT and the ALCL on this, it goes back to the melanoma, for example, with pembro and nivo. If you look at the dosing recommendations for pembro, this will go to 2 per kilo for more than 12 years of age, but you may be underdosing some patients because the maximum dose is 200. When you go to nivo, they say everybody above 12 gets whatever the dose is, 480 or whatever it is.

How did those decisions come about, and is there an advantage of starting with a fixed dose in certain populations in which you have the same disease entity that you see in adults, and to expedite the development of these novel therapies in pediatrics?

DR. FOX: I agree that in certain situations, fixed dosing for patients over the age of 12 may be very appropriate and collection of pharmacokinetics to ensure that we are where we think we are. To the point about targets and

getting to the right target concentration, I think this is really important, particularly as many of our drugs for children with cancer are in some ways repurposed, by the targets are not quite the same. That's clear from crizotinib; you're pointing it out for melanoma. These are the types of things that we have to be very careful to clearly describe, and to the extent possible, put preclinical data around to help support dosing decisions.

I will also point out to my point, that any time you do dose per weight, you are likely having a systematic dose reduction, which is weighted toward that dose reduction in the smallest of people. We saw that with trametinib. We see it consistently when you compare per kilo dosing to per meter squared dosing. And I'd love to be in a position to be able to look at comparisons of what would happen if we did meter squared dosing instead of per kilo dosing. Thank you.

DR. PAPPO: Thank you very much. No further questions.

Donna Ludwinski is next.

MS. LUDWINSKI: Thank you. Donna Ludwinski, patient representative.

I just wanted to ask you, Dr. Fox, to comment on any additional challenges that you think are relevant to this conversation about CNS tumors. I noticed in the draft guidance there wasn't anything specific about brain tumors and what other considerations there might be.

DR. FOX: Yes. There are definitely considerations when we're considering children with brain tumors, which, as Dr. Blackman reinforced, is the second most common cancer in children in the United States and the leading solid tumor in the United States. Obviously, and as most on this call are aware of, the determination of the penetrants, or the likely penetrants, of the drug into the tumor is really important, the blood-brain barrier as it's called.

The other considerations on the practical front are do we actually know what the targets are? Are we in a position to increasingly biopsy

patients to determine if they have the targets of interest for specific drugs? And, really, dosing in children with brain tumors, I use the example of concomitant medications, dexamethasone, that was specific for many of our children with brain tumors, where their body weight and their lean body mass are completely disconnected because of long-term use of corticosteroids. Those are some of the issues.

Other issues include issues with swallowing and being able not only to have a liquid formulation, but a liquid formulation that has been [inaudible - audio gap] with an NG tube often is necessary in that population. Thank you.

MS. LUDWINSKI: Thank you. That's all.

DR. PAPPO: We have time for a final question.

Dr. Yoram Unguru?

DR. UNGURU: Thank you. Yoram Unguru, Children's Hospital at Sinai and Johns Hopkins Berman Institute of Bioethics. My question is for Dr. Blackman.

Thank you for your presentation. Thank you for raising issues related to cost and risk. Your last couple of slides, Dr. Blackman, you mentioned the illusion of precision and how this relates to safety and risk. I wonder if the assumption is that we leave well enough alone and we don't strive for that higher bar, recognizing what some of the issues are. How do you envision, actually, achieving this in practice? And specifically, what role do you see for the disease community, and patients, and patient-centered kind of views, if you will? Thank you.

DR. BLACKMAN: Thank you for the question. It's a very thoughtful question. I want to, again, just highlight, I think that we absolutely should strive for the bar, but I think it's a matter of, again, how do we prioritize our efforts? It's balancing on one hand the potential of moving something forward to approval and getting patients to have access, even if it may not be perfect in terms of our knowledge and understanding around dose versus spending time, and effort, and

resources, and maybe not being in a position to move something through to approval until it's perfect, and I do believe that there's a third way.

I think that it's essential, both within industry and certainly for the forces that regulate industry -- recognizing that targeted therapies may be administered to patients over a long period of time and may have an impact on development -- to hold our collective feet to the fire in terms of collecting post-approval to try to understand the long-term outcomes of these drugs in development. I think that as long as those studies are going to be done, they should be funded appropriately, executed appropriately, and the data should be made available.

I think that part of that can include getting sparse PK data and obviously knowing when to sample based on the work done during development, but collecting that data over time and being able to correlate that data with long-term side effects, and certainly with efficacy, and beyond just surrogates for efficacy such as

response rate, but really begin to think about things like correlating dose to things like longer term assessments such as time-dependent measurements like overall survival or progression-free survival.

What's really essential, I think, in order to achieve that is making sure that patients, post-approval, are enrolled on registry trials, and that that's something not just requested by or expected by the broader pediatric oncology community but also supported. Patients should be enrolled. I think another, of course, essential component of this is centralization of that data and making sure that we do have a way of capturing that data across centers, and that it's not siloed in single institution studies or small cooperative group studies but really represents an effort to capture data around how that drug performs in children; what the long-term safety outcomes are; what the relationship is between exposure and efficacy or exposure in long-term toxicity, and it really is going to take a community effort there.

But again, I think the agencies that regulate our industry should ask for long-term follow-up studies. They typically do, but tying that to an assessment of PK, and PK and safety, and PK and efficacy is a marginal cost on that, provided, of course, we have those PK assays available for a longer time frame and that people enroll on those registry studies.

DR. UNGURU: Thank you, Dr. Blackman. I have no additional questions.

DR. PAPPO: Thank you very much.

I want to thank all of our speakers, both our guest speakers and the FDA, for their excellent presentations. I'm sure that we're going to be reaching out to you again after the OPH session for additional clarifying questions.

We will now break for lunch. It is 12:43 p.m. Eastern Standard Time. We will reconvene at 1:15. 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 1:05 p.m. to ensure you are connected before we restart at 1:15 p.m. Thank you very much, and enjoy your lunch.

(Whereupon, at 12:43 p.m., a lunch recess was taken, and meeting resumed at 1:15 p.m.)

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

(1:15 p.m.)

Open Public Hearing

DR. PAPPO: Welcome back. I hope you enjoyed your lunch. We will now begin the open public hearing session.

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

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

meeting.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, please unmute and turn on

your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing, for the record. You have five minutes.

MS. PHILLIPS: Hi. My name is Sophia Phillips, and I'm a health policy associate speaking on behalf of the National Center for Health Research. Our non-profit think-tank scrutinizes research on the safety and effectiveness of medical products, and we do not accept funding from companies that make those products; therefore, we have no conflicts of interest.

We strongly support the safety and tolerability specifications identified in the January 2023 draft guidance included in the FDA briefing document. It is essential that duration of exposure, dosage interruptions, and adverse events be compared across varying dosages. We agree that safety monitoring rules should be prespecified for trial designs. We also agree that adverse reactions, even those considered less

severe, should be carefully assessed and considered when selecting the dosage for follow-up clinical trials.

We also strongly support the statement that population pharmacokinetics, or PK, data should be evaluated to identify specific populations; for example, defined based on weight; age; sex; race and ethnicity; or organ impairment, in which the PK demonstrates clinically meaningful differences in exposure. However, the September 2022 Guidance on General Pharmacology Considerations provided a more detailed list of important variables to consider such as calculated BMI; gestational age; postnatal age for neonates; and laboratory tests, reflecting the function of organs responsible for drug elimination. We urge that these be added to the new guidance on dosing.

It is also essential that these variables not only be evaluated separately; instead, relevant covariants should be incorporated into analyses to identify potential differences in safety or effectiveness for relevant subpopulations. For

example, within an age group, there may need to be different dosages due to weight, sex, age, race, or ethnicity. While this does not require a substantial number of patients representing these different groups to be enrolled in a study, it is better to do that prior to a drug approval of particular doses then to find out the dosages are too high or too low for some groups years after the product is approved.

The proper use of covariants and phenotype data was clearly expressed in the September 2022 FDA Guidance on General Clinical Pharmacology Considerations. Unfortunately, it was not included in the January 2023 guidance specific to dosage optimization, and it should be added to that guidance as well. Thank you.

Clarifying Questions (continued)

DR. PAPPO: Thank you very much.

I believe we only have one speaker; therefore, the open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience.

We have quite a bit of time to have some additional clarifying questions. We still have all of our speakers here, so 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 the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Dr. Frank Balis will be the next person to ask a question.

DR. BALIS: Thank you, Dr. Pappo. This is Frank Balis. I had two things to raise. One is a follow-up on Dr. Glade Bender's question about

therapeutic drug monitoring in dose-finding studies.

Obviously, in doing therapeutic drug monitoring, there's an implication that there's a target range that you want to achieve, which we would rarely have in the setting of a dose-finding study and, in fact, we've been using drugs to treat cancer for many decades, and there are few exceptions of drugs that we actually have defined a therapeutic or non-toxic range for in order to apply therapeutic drug monitoring to their use.

That being said, one of the options potentially for doing this is looking at preclinical studies and concentration ranges that were effective in models. This is obviously a risky prospect to do because there are things that occur in the patient, i.e., protein binding, that we don't account for when we measure drugs. We generally don't measure pre-drug concentrations, so there's a risk that that could put us in the wrong dosage range.

A number of decades ago, there was a

short-lived attempt to do drug concentration escalations in a phase 1 study; that is, patients had their doses adjusted to achieve a specific concentration narrow range, and then that concentration range was subsequently escalated in groups of patients; short-lived I think, in part, because of the technical issues in doing it. But if we use that approach, we actually might even be able to define a therapeutic range for subsequent therapeutic drug monitoring. So it's an idea that has been around for a long time, and one that we might want to revisit in terms of its potential utility.

What it does do when you do this type of an escalation is essentially to limit the amount of intra-patient variability, which is a particularly big problem in pediatrics because of the narrow dosage ranges that we use. So when we escalate a dose by 30 percent and the intra-patient variability is greater than that percentage, there's going to be considerable overlap, at least in the concentrations achieved, and it's going to

be less likely that you're going to actually be able to see a difference in dose levels, and more importantly, define a dose-response relationship.

The second thing I wanted to mention is that there was a mention in Dr. Wessel's talk about extrapolation, which I was happy to see in Dr. Fox's talk that she struck a line through it. I don't think that that should play much of a role in defining the optimal dose in kids. And again, we go back to our experience in current anti-cancer drugs -- which had been developed over many years in phase 1 studies -- that have excluded the youngest and probably most vulnerable population from participation in those trials. And when we extrapolate it down to those younger age groups using a very crude tool for adaptive dosing, meaning body weight or surface area, many of those patients got hit, sometimes significant and severe toxicities.

So rather than extrapolating, we need to study the patients in all age groups in defining the optimal dose and understand that our current

methods of adapting the dose using some measure of body size is inadequate in many cases. That's all I have. Thank you.

DR. PAPPO: Thank you, Dr. Balis, and some of this discussion can probably be also highlighted again when we go to the specific questions. Thank you very much for your insights.

Dr. Mody, you're next.

DR. MODY: Yes. Thank you, Dr. Pappo. I'm Rajen Mody from the University of Michigan, pediatric oncology, and my question is for Dr. Fox and other FDA panel members.

For all these years of doing pediatric oncology, we are always told that the number of patients that you need to make any decision, based on pharmacogenomics, is very large, and we just do not have enough data. And now with the Molecular Characterization Initiative, the CCDI, and other initiatives where we are depositing -- our institution, as well as several others -- thousands of patients germline data, are we finally reaching that point? Are we there yet, where we can

actually make some informed decisions based on pharmacogenomics? Thank you, and I'll take my questions off.

DR. FOX: I didn't touch directly on pharmacogenomics in my talk, but I think the point is very well taken. Carefully curated data for rare patient populations is vitally important for advancing the field of pediatric oncology. These are long-term efforts, and I think the validity of those efforts needs to be held in the consistency with which we do it and the adequate clinical annotation of those samples.

Obviously, as you mentioned, there are efforts to do that with NCI and others. I believe that your work, and the work of others in the field, that the ability to do genetics, and targeting, and the MATCH study, ICAT, and other studies, have really demonstrated that national, and even international, approaches to collecting genomic data -- not only somatic but also germline -- is critically important to how we move forward, not only for targets, but for toxicity and

late effects in children with cancer. Thank you.

DR. MODY: Thank you, Dr. Fox.

DR. PAPPO: Dr. Glade Bender?

DR. GLADE BENDER: Hi. Yes. Thank you. Julia Glade Bender from Memorial Sloan Kettering. I think my question is to Dr. Fox and Dr. Blackman, who sort of present two sides of a coin in that the unified goal is to develop drugs sooner in pediatrics and decrease the lag, but then there's the question of formulation and the cost of formulation. Dr. Fox so beautifully showed the difference between the development timeline of larotrectinib and entrectinib, and the difference there being formulation.

So with all of the regulation related to trying to speed the approvals of and testing of pediatric drugs, the Race for Cure has a molecular targeted list, but clearly some targets are more relevant than others, and maybe there's, as opposed to not an if but when, some direction needed for companies to know that the when is sooner in some drugs than other drugs; and where does the

responsibility lie in terms of informing those kinds of decisions?

DR. FOX: Hi. Beth Fox from St. Jude. It's an important question, Dr. Glade Bender. I started with the analysis and the table that shows the common ages of childhood cancer because that truly is the starting point. So from my perspective, when I look at a target that is likely going to be important in a tumor, for example, like neuroblastoma, we know what age group those children are and the ability to understand the formulation.

I will go back to the example of crizotinib. We had access to that agent very early in development, and as you saw, the pharmaceutical partner developed four different formulations during the course of a phase 1/2 study, and we tested all of them with PK. And in the end, we ended up with a formulation that we tried to administer to small children with neuroblastoma in the upfront setting, and it was considered not palatable, and that study was amended, in part,

because of that palatability and, in part, because the development of next-generation ALK inhibitors, but I think it's an important question.

I think, in my mind, the way to start, as Dr. Wessel indicated, is probably not crushing tablets because that adds layers and layers of variability, but I do think intermediate formulations could be considered. And in my mind, as I develop development plans for drugs, it's about what the commitment is longer term because none of us want to see resources put in that can't be realized if the drug isn't moving forward. But those discussions about is there a commitment to begin to develop that, and are our pharmaceutical and chemical partners really working to think about what ultimately in their lead compound will be soluble, and what are the options ultimately for formulations, I think those are conversations we could start having earlier.

I'll turn it over to Dr. Blackman.

DR. BLACKMAN: Thank you, Dr. Fox. Thank you, Dr. Glade Bender, for the question. It really

is challenging, I would argue, to determine what's the right time to begin investing resources in [indiscernible] pediatric formulation development.

There's clearly a point at which I think it's almost indefensible to not do it, and that's certainly when you've got proof-of-concept data for the lead indication, which, as you know, in many instances, this is going to be an adult indication, and there's relevancy of the target to pediatric cancer, and you've got evidence of efficacy. I think, at that point, it would be very hard to defend a position of non-investing resources in pediatric formulation development.

Depending, of course, on the characteristics of the molecule, that may be easier, it may be harder, it may take months, it may take years, which of course is a challenge. And knowing that as you move to the left in the time line, before you've got proof of concept for pediatric indication, especially if that indication is different than the adult education, or before you've got proof of concept in the adult

indication, and you don't know if the program's even viable, it is really, really hard, I think, for many of us who are champions for pediatric drug development within industry to be able to convince people to allocate the resources necessary when you don't even know if the drug is going to move forward. So it's going to end up being somewhere along that spectrum and, of course, it will never be early enough.

So I do believe that sometimes we're going to be forced into a situation of good enough, where we have to work with extemporaneously formulated molecules. I would agree with Dr. Fox that simply crushing tablets is probably not ideal, and we may need to work collectively to come up with solutions to get molecules into children who are too young to swallow tablets or to run trials in children who can only swallow tablets -- again, not optimal -- to get us to that point in time where we know that there's a path forward for development in adults, something to really then make those regulations and incentives sticky.

Certainly before we really embark on mid-stage studies in children, you want to go in with a pediatric formulation wherever possible and not make it something that -- I think ideally we don't want to see it done as a postmarketing commitment. We'd like to see that done pre-approval, but the timing part is difficult. There's no one set answer, so it's always going to be on a case-by-case basis, I suspect.

DR. PAPPO: Does that answer your question?

DR. GLADE BENDER: Thank you. I think that's very clear.

DR. PAPPO: Yes. I'm Alberto Pappo, and I had a question for Dr. Wessel, and if you wouldn't mind just expending a little bit on the concept of trials using dose selection strategies.

Do you think that this is an optimal way or a good way to try to identify an optimal dose, and are there any significant limitations? For example, does this increase the sample size; are there any considerations regarding the starting dose; and what levels should be explored? I just

wanted to hear your thoughts about this potential strategy.

(No response.)

DR. PAPPO: I don't know if Dr. Wessel is still on.

DR. WESSEL: Sorry. I was trying to get my microphone unmuted.

DR. PAPPO: Thank you.

DR. WESSEL: Thank you for the question. I think that these dose selection trials need to be done, and the strategy needs to be done, on a case-by-case basis. I think Dr. Donoghue also had a comment on it, but I might let her elaborate if that's ok.

DR. DONOGHUE: Thanks, Dr. Wessel.

Dr. Pappo, were you referring to a specific slide that Dr. Wessel presented when she presented the alternative, the example of an alternative dose-finding strategy where she discussed looking at two different dosages? Is that the slide you were referring to?

DR. PAPPO: That was the slide, yes. I

believe that was the slide. Correct, yes.

DR. DONOGHUE: Okay. We presented that as an example, thinking a little bit along the lines that as you are accumulating data in your initial phase 1 dose-finding trial, you're able -- based upon pharmacokinetics, pharmacodynamics, and perhaps some early activity data, although we understand that's not always the case at that point given the small numbers -- to identify or hone in on a target dose range that appears it might provide the best balance between safety and efficacy. In those cases, choosing those, perhaps, two different doses to study a bit further prior to enrolling a large number of patients in a trial intended to support safety and effectiveness seems appropriate.

However, that is simply an example. And as others have pointed out, we have to really be thinking about the dosage optimization process along a continuum. We wouldn't advocate picking two doses at random to study if we don't have sufficient data to support why we would want to

pick those two doses and what pieces of information we feel are still needed to help provide a reasonable degree of assurance that the dose will provide the best benefit-risk balance patients.

We're not advocating for that type of design until we have proof of concept that a drug actually is worth moving forward into further development. We really need to have a certain amount of information to make informative decisions and provide advice about what type of further dosage optimization may or may not be necessary and how best to do that. So building some flexibility into early trials so that you can backfill different dose cohorts might make sense. There are a variety of different ways we can build this into the process.

I do want to emphasize a little bit some of the nuance in terminology that we're using. One thing that I was hearing -- and I really appreciate, Dr. Blackman, your last quote from Voltaire basically saying that we don't want perfection to be the enemy of the good. We're not

expecting that we're going to find a perfect dose necessarily for pediatric patients, or even adult patients with cancer, through the information that we acquire along drug development. What we're really looking for is a thoughtful process during development that's reacting to the information as we aggregate it, and trying to fill in the gaps in knowledge, so that by the time we're embarking upon a large-scale trial, we have a degree of reassurance that the dosage is reasonable that we're not going to run into problems later with large amounts of dose modifications and reductions, if we can avoid it.

Ultimately, we feel like that approach really helps de-risk a development program in addition to being the best thing for patients. But again, that's why we emphasize the importance of meeting with us frequently and as early as possible so that we can review together and consider the information that we have and adapting, if we need to, a development program to try to acquire that information that we think is needed.

We do have examples in the adult oncology space, in particular, where we thought we had known the right dose, we've approved a dose, and then ultimately have had to pull drugs off the market due to excessive toxicity and impacts on survival. We want to minimize that scenario as much as we possibly can, understanding that we do have limitations with sample sizes. We have limitations in our degree of scientific knowledge, and sometimes we do need a degree of information to be accumulated postmarketing as well to further understand the relationship between dose and efficacy and safety.

But I do want to emphasize that we intend on continuing to exert regulatory flexibility as we have done in the past; case in point, the trametinib approval for ALCL, where we had a postmarketing commitment for further dose and understanding different dosages. We're not saying that we're going to unnecessarily hold up an important approval that has a potential to make a big impact for patients if there are outstanding

questions for dosing, provided that we know and have confidence that the overall benefit-risk assessment is positive.

DR. PAPPO: Thank you. No further questions.

Dr. Frank Balis?

What about Holly? Did you have your hand raised? Did you want to ask a question?

DR. BALIS: Yes.

DR. MEANY: Dr. Donoghue answered my question. Thank you.

DR. PAPPO: Okay. Thank you.

Frank, go ahead, please.

DR. BALIS: Thank you. This is Frank Balis. This is for Dr. Blackman.

Could you give us a range of the cost to the company to develop a pediatric formulation? And secondly, if there was magically a central facility that was in place to do that job for a variety of companies, would you provide your compounds, your drugs, to a facility like that to have it done?

DR. BLACKMAN: Thank you for the question,

Dr. Balis. I can provide a rough example, some rough figures from a program that I've been recently involved in maybe just to give you a little bit of history on this. This is a remarkably insoluble kinase inhibitor. The company that had rights to it before evaluated 17 different formulations to try to solubilize this molecule. In fact, when we talked to them about it, their first question to us -- having exhausted all available ideas that they had, they had one final idea, and asked us how much olive oil they thought a child could drink because they found that the drug was soluble in olive oil, which was an interesting question to be asked by a CMT person.

The pediatric formulation ultimately came to bear, but it was a low single-digit million cost, and that cost is more than just the initial [indiscernible] chemistry. It's also the manufacturing, all the lot testing stability, all the regulatory CMT work that goes with it, along with an actual clinical trial or relative bioavailability/bioequivalence that needs to be

done, and any preclinical testing that needs to be done as well.

So none of these things are just sort of -- as you and, I'm sure, many of the people here know, launch is sort of done on the benchtop, and then moved forward into the clinic. There's an immense amount of antecedent work, both nonclinically and clinically, that's required.

I'm sorry. The second part of your question there, Dr. Balis?

DR. BALIS: The second part was, if there was a central facility, perhaps government supported, would you give them your drug to develop a pediatric formulation?

DR. BLACKMAN: I think, certainly, if there was a central facility that had expert pediatric formulation development, I think a lot of sponsors would be really keen to do that. There are a small number of private facilities. Bend Research out in Bend, Oregon is particularly good at this. But I think, certainly, if there was some centralized locus of expertise, I could imagine certainly

wanting to work with them if there was a way to do it in an expedient time frame.

Of course, one of the challenges with anything when you outsource the work -- and it doesn't matter if it's to a government partner or if it's to a private partner -- is making sure that that work is done in such a way that at the end of the day, that work can be submitted as part of your NDA to support the potential approval. Obviously, it has to all be done GMP compliant.

So I think if there were something up to par with that, and of course contracting and all the other things operated on a time frame that was reasonable -- and of course when you're working with the government, there's also IP considerations. If there was some idealized way to make it work, I think a number of sponsors might be interested in taking advantage of a centralized pool of expertise. Thank you for the question.

DR. PAPPO: Next is Dr. Malcolm Smith.

DR. SMITH: Thank you. It's Malcolm Smith, NCI. A question, going back to randomized trials

and the comments from Drs. Donoghue and Wessel, the question is about the trade-off between the small patient populations that most of these drugs will be developed for, and doing a randomized trial, and the trade-off in thinking about a particular patient population and what's the next most important question for them versus from the drug's perspective, and how it might best be developed for that indication and what's best for it.

With crizotinib as an example, defining the dose of crizotinib better for a particular population may be important, but maybe for neuroblastoma, the important thing is to study lorlatinib rather than crizotinib. So that's a trade-off, and how is that trade-off evaluated? Because if you prolong this optimization, maybe that means another agent won't be studied for that population if you prolong this optimization, and getting the combination testing might be delayed. So I understand there's flexibility, but how does that flexibility get operationalized when there's such small populations? There are lots of

questions that could be asked that may be important within those small populations.

DR. DONOGHUE: Thanks, Dr. Smith. I just want to repeat the question just to be sure I have it right. Are you asking how we approach decision making with respect to the approaches to dosage optimization in light of small numbers of patients, and thinking about balancing pragmatism with the need or desire for new information?

DR. SMITH: Right. From a standard phase 1 trial, you'll have some evidence for tolerability. You might have done an expansion or the recommended phase 2 dose, what you think is the recommended phase 2 dose. You're going to have data from adults. You're going to have PK data. So you'll have a body of data that may produce a good enough dose, but then there's the question of what would go into the decision of a company thinking, "Oh, no. That's not good enough. I need to do more" to determine the dose more precisely for this population, as opposed to all the other things that might be done for a group of patients with relapsed

neuroblastoma and another drug that might be studied, or moving directly into combination testing.

DR. DONOGHUE: I think what you're highlighting, or at least what I'm hearing from you, Malcolm, is you're highlighting the complexity of these decisions. To me at least, you're also highlighting the importance that we have multistakeholder discussions along drug development in pediatric oncology when we collectively as a community are determining what the drug development program should look like, and to be aware, to the extent we can be, that a decision we're making does not have unintended consequences, A; and also that we are really clear about what the question is that we think is important to answer, and that we are asking for the information that will answer that important question, but not necessarily, I think as we said before, having a knee-jerk response asking for additional exploration and a certain number of dose levels in a certain way without really understanding why we're asking for that.

So I think this really has to be part of an ongoing discussion. The process of dosage optimization really is a multidimensional process that needs to take into account all of the information that we have. And sometimes during early clinical trials, there is really valuable PK/PD data that sometimes isn't available until some period of time later. The extent to which we can leverage every piece of information that we're collecting in the early phases to help inform our decision making about what dosage optimization looks like and what additional amount of work is necessary or important to do, I think are decisions that we have to make along the way.

And it will not look the same for every drug because some drugs may have from the very beginning, such as larotrectinib, very clear evidence of effectiveness in a rare population and early investigation in those young pediatric patients that help streamline drug development. Others, we may have a lot more information about drugs, in the same class even, that can help inform

the decisions we're making.

But I think the points you bring up are important, and we really need to be thinking about all these things as we work together to determine the best approach to take for a given drug development program.

DR. SMITH: Okay. Thank you.

Dr. Ted Laetsch?

DR. LAETSCH: Thank you, Dr. Pappo. Ted Laetsch. I was just going to piggy back a little bit on Dr. Smith's question and highlight again, as Dr. Blackman highlighted, that there are multiple agents in-class and expanding numbers of agents in-class for many of these rare pediatric indications.

I would ask and highlight the FDA's thoughts on how to ensure there's international regulatory alignment on the requirements for studies of these drugs. Many of these drugs are studied in broad international clinical trials to achieve a sufficient number of patients with rare pediatric indications, and I think it's really important,

clearly, that we have alignment on the requirements so that we don't inadvertently delay drug development for children by having extensive dose finding of multiple agents in the same class for our very rare patient population, for example, when that may not answer the most important question, as Dr. Smith highlighted.

That was sort of a question for Dr. Donoghue, and I appreciate having the EMA on, but how do you think about aligning these requirements across regulatory bodies?

DR. DONOGHUE: Thanks, Dr. Laetsch. I want to just emphasize, first of all, that in terms of regulatory requirements in the United States, our requirement under PREA, as amended by FDARA since August 18, 2020, is that we have the authority to require a molecularly targeted pediatric cancer investigation for targeted drugs that are being developed in adults that are working against a target that we think is substantially relevant to one or more pediatric cancers.

That's the degree of our regulatory

authority, and what that would look like is an early phase 1/2 clinical trial in pediatric patients. It is not a requirement for dosage optimization or to optimize the dosage. We don't have any regulatory requirements, per se, that I'm aware of, that relate to optimized dosages. The regulations that we are bound to ultimately when we're thinking about approving a drug is that we have to have substantial evidence of effectiveness and we have to a have a positive benefit-risk relationship such that we think the drug is appropriate to approve. I think if you have an optimized dosage, there's an increased likelihood that you're going to have a positive benefit-risk relationship because you'll have less toxicity, as I mentioned before. But in terms of the pediatric requirement, we do not have a requirement for extensive dose evaluation.

Having said that, I acknowledge and I completely agree with the need for us to collaborate as much as we possibly can with our other global regulatory agencies in order to align

as much as possible in the advice we're giving for pediatric oncology trials. We do that quite regularly. In fact, we had a meeting from 7:30 to 10 yesterday, working on issues related to that with EMA and other regulatory agencies, so it's something that we do take very seriously. Are we perfect at it yet? No, we're not, but we have continued commitment to improve that.

It actually would be very helpful to have as much feedback as we can get from the community and as much interaction we can get with the community when we're all talking together, industry, investigators, advocacy, regulators. The more communication we can do together on that, I think the higher likelihood that we're going to make decisions that are not competing with one another, or obstructing drug development, or wasting resources, patient and financial resources.

DR. LAETSCH: Thank you. I appreciate the answer and appreciate the collaboration.

DR. PAPPO: Any additional clarifying questions?

(No response.)

Questions to the Subcommittee and Discussion

DR. PAPPO: Okay.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording.

We will now proceed to our first question, which is a discussion question. Can I have the slide for the first question? The first question is, Discuss the unique considerations associated with dosage optimization in pediatric oncology.

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

(No response.)

DR. PAPPO: Perfect.

Let's start with Frank.

DR. BALIS: Thank you. Frank Balis from CHOP. Having done this for a number of years, I think we've talked about already today that we really have moved on substantially in the types of drugs that we're developing, the selectivity that they have, but we have not moved on in terms of how we study those drugs in the clinic. I think the biggest roadblock to moving on is the endpoint of the dose-finding study.

Obviously, toxicity is relatively easy. In most cases it occurs rapidly. It's relatively easy to score it, particularly with the grading criteria that we currently have, but it's also probably the most compound endpoint you could ever have. It's, what, 800 and some terms in the CTCAE? For example, grade 3 hypophosphatemia is not equivalent to grade 3 brain necrosis as toxicities.

So there are problems with it from the perspective of if we want these drugs to be dosed

in a way that's less toxic, which was the whole point of developing targeted therapy, we've got to find better endpoints for determining what the optimal dose is. We're faced with the choice, in addition to toxicity, of using therapeutic endpoints, which has always been an issue. It may be less so if the dose-finding study is done in a selected population that includes patients who have the target for which the drug is developed for.

In the past, we've always done these studies in a broad range of cancer patients, and the sensitivity of individual types of cancers may be different, and even in patients with the same type of cancer, the sensitivity can be different. And the endpoint of response is one that is delayed, sometimes significantly out, which makes it also difficult to use as an endpoint.

So that basically brings us back to using pharmacologic endpoints, either pharmacodynamic or pharmacokinetic. Pharmacodynamic is closer to a clinical therapeutic endpoint, but has some limitations in the sense that it's difficult in a

pediatric population to sample the tumor and to look at pharmacodynamic endpoints. And using surrogate tissues like blood cells may not reflect what's going on in the tumor for a variety of reasons, including the fact that mutated targets may not have the same binding affinity for a drug that we're studying.

Pharmacokinetic endpoints may have some advantage in the sense that it's relatively easy to sample. It kind of goes back to the comment I made earlier about therapeutic drug monitoring in terms of having a therapeutic range that is defined that we can use to determine if we've reached the optimal dose, but pharmacokinetic endpoints addresses the variability, which is an issue, and we can significantly limit that by using drug levels to adjust the dose.

There are other ways around, including, for example, with older drugs, we just pick the range that many patients have, knowing that that drug has been therapeutic for a while, so that could be done in retrospect; or also using information from

adults in terms of defining a range that we can target, at least knowing the dose that would get us to the point that we get similar exposures to what occurs in adults.

So I think if we're going to take the next step, we've got to move on from simply using toxicity as a simple way to determine whether the dose we've reached is optimal or not. Thank you.

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

Julia Glade Bender, you're next.

DR. GLADE BENDER: Just to speed things along, I will state the obvious. I think what has come across to me as the number one issue -- thank you, Dr. Beth Fox -- is formulation is the most unique consideration associated with dose optimization in pediatric oncology. It's absolutely clear that it's hard to study dosage optimization when you're not even delivering the dosage you think you're delivering because you are limited by tablet size and you have overlapping doses.

If we are to optimize dosage, we need to

actually have more precision in the doses that we deliver based on formulation. So again, I think this point of when the formulation is developed and for which drugs is really critical. I don't think, as Dr. Blackman said, it should be a requirement at the onset for every drug, but certainly for those drugs where there is an early signal or an overwhelmingly strong biologic rationale, it should be earlier than it currently is so that we don't delay the process.

DR. PAPPO: Thank you very much, Dr. Glade Bender.

Steve DuBois?

DR. DuBOIS: Steve DuBois, Dana-Farber. I guess two points come to mind. Of course, the rarity of the populations that we're treating and studying as part of any dose optimization activity in pediatric oncology really, I think, poses a substantial challenge when we're designing these types of studies. Then I like that Dr. Fox brought up the the biology and the biological differences between maybe adult and pediatric type tumors. She

provided the example of crizotinib, which for a neuroblastoma indication was really requiring a higher dose to target a mutation rather than an ALK translocation as would be seen in adults with non-small cell lung cancer, where you'd expect a translocation to be more sensitive.

So I think those are other important considerations that maybe extrapolating completely from the adult dose may not be biologically appropriate, depending on what we're asking of the molecule.

DR. PAPPO: Thank you very much.

Dr. Smith?

DR. SMITH: Yes. Malcolm Smith, NCI, and just a couple of points about distinct unique considerations. One, again, is the small patient populations, and that there is an opportunity cost if one is going to do a prolonged dose optimization in these small populations. I think that suggests that we really want to reserve prolonged dose optimization for those settings in which the evidence is clear that we need more tolerability

and PK data or something, beyond that that we typically would gain from a first-in-child study and from the adult experience that we had; and Dr. Blackman to be quoted here, "Don't let the perfect be the enemy of the good."

Another point is distinctive, that as opposed to some adult cancers, the ultimate goal of bringing agents into pediatric testing is to cure more children, so that goal in the end is maximizing the ALK cell [indiscernible] agent; so to be cognizant that even small reductions in the activity of the agent may have substantial impacts if the goal is cure.

The last two points really apply both to adults and pediatrics but, again, the point that there are some agents that we will know from the adult experience and from the preclinical data that we will never get to the drug exposures in children that would be associated with optimal responses, and that we will be stopped by toxicity from getting to those doses; so determining what those agents are and prospectively saying, "Okay. This

is that type of agent, and we will escalate as far as toxicity will let us escalate."

Then the final point, and it was made in, I think, Dr. Wessel's presentation, is about the importance of looking at these chronic toxicities and chronic low-grade toxicities that many of our targeted agents are given on a continuous basis. I think that's a really important issue. We don't need randomized trials to look at it; we just need to incorporate it into all of our dose finding and get away from the kind of acute cytotoxicity dose finding for these agents that we expect to give on a chronic basis, and for which a low-grade toxicity lasting for weeks will not be tolerated by children.

DR. PAPPO: Thank you, Dr. Smith.

Dr. Laetsch?

DR. LAETSCH: Thank you, Dr. Pappo. I was just going to build off what Dr. Smith said. In pediatrics, we're really looking for agents with large effect size that can hopefully increase the number of patients who are cured, and this is

really necessary given the small patient population, and it's going to be very challenging to show small statistical differences in outcomes of patients, so we're looking for agents that are highly active.

So I think building on Dr. Donoghue's comments in response to my question, I think it's important to think about for which drug this is important, and that early-phase trials may find a good enough dose to study and try to prioritize agents across patients. Then as Dr. Smith suggested, considering more in-depth dose optimization, really, for those agents, where it's clear that it's necessary and clear that they're hopefully likely to move forward in pediatric oncology so that we don't commit resources and ask a large number of patients to enroll on clinical trials to define a dose of a drug that will not move forward. That's clearly not optimal for the field.

DR. PAPPO: Thank you, Dr. Laetsch.

Dr. Meany?

DR. MEANY: Holly Meany from Children's National. I just wanted to bring up a point that Dr. Wessel mentioned, and I think Dr. Fox also showed some nice data, that we are having a much higher number of patients surviving their cancer and their therapy, and late effects years down the road are important considerations for a lot of these agents, particularly more targeted agents that patients may remain on for an extended period of time. I think that's an added challenge in our pediatric population, and certainly these late effects that would affect our children are not things we might garner from adult trials. Thank you.

DR. PAPPO: Thank you.

Dr. DuBois?

DR. DuBOIS: Steve DuBois, Dana-Farber. I should have said this with my first set of comments. I know we'll get to this as one of the dedicated questions, but just to say out loud that so much of the success that we've had in pediatric oncology has been due to combination approaches,

and I think culturally our field has a strong desire to get two combinations relatively quickly, sometimes even as part of the first-in-child clinical trial. So I think that's another important unique consideration.

DR. PAPPO: Thank you.

I'm going to try to summarize the 655 comments, and if I miss something, or if I misinterpreted something, please feel free to chime in.

It's apparent that the types of drugs that we're using now to treat childhood cancer have evolved from the classic concept of cytotoxic chemotherapy and we need to be shifting the way we study them. Perhaps the endpoint of toxicity by itself might not be the right endpoint that we should be using for these drugs. We need to find better endpoints to assess the efficacy, and the toxicity, and the optimization of these drugs in pediatric patients.

It is important also to identify the target population that is perhaps optimal for dose

finding, and that perhaps using other endpoints such as PD might be a good way to proceed; however, that might be a little bit problematic in pediatrics. We can continue with PK and using therapeutic range dosing for selected agents.

Another issue that needs to be taken into consideration is the formulation for these patients and for dose optimization that might have significant challenges in specific populations. Also, we need to recognize that it's challenging to test these drugs and optimize doses because it's a rare population of patients. The biology of those diseases might be different than from adults, and we cannot extrapolate sometimes the data that we see in patients.

Another point that we need to highlight is that when we are trying to explore a drug that may have activity in pediatrics, we're really aiming for a cure, and we want to see big differences when we try those drugs. So it is important to optimize those drugs in specific populations. There's nothing wrong with having a small phase 1 trial to

try to identify the dose, but if we find a level of activity that is significant in a specific population, that's where additional studies can be done to optimize the dose on these patients. We are also, again, looking for a large effect of these drugs, and we need to be also aware of the fact that some of these medicines are going to be given in a chronic dosing in these patients, and we need to be aware of the potential side effects that these patients can have with chronic exposure. I think that's about it.

Did I summarize everything or did I miss anything?

(No response.)

DR. PAPPO: So there are no comments, so now we will move to question number 2, which reads, discuss the potential challenges to identifying an optimized dosage for new drugs and biological products for pediatric cancers and potential strategies to address these challenges.

(No response.)

DR. PAPPO: If there are no further

questions or comments concerning the wording of the question, we will now open this question for discussion. I think that some of the issues are going to be similar to question number 1, but I look forward to your comments.

Dr. Julia Glade Bender?

DR. GLADE BENDER: I want to revisit one of the challenges that was brought up earlier by Dr. Wessel, which was the difficulty of doing postmarketing studies and testing agents that have already been FDA approved. I think some of the recent pediatric studies in the postmarketing space, particularly with larotrectinib, have accrued remarkably well in the pediatric population. These drugs are not so easy to obtain, and the idea that they can be obtained through a trial free of cost and that the patient is contributing to knowledge is appealing to families. I'm not sure that that's actually a challenge, to do it in the postmarketing setting, so I think in many cases that is a good strategy going forward.

DR. PAPPO: Thank you very much.

Andy?

DR. KOLB: Thank you, Dr. Pappo. Andy Kolb, the Leukemia and Lymphoma Society. I think one of the challenges is that many of these initial studies are publicly funded, and we will have smaller cohorts with fewer resources for the optimization that I think is inferred from Dr. Wessel's presentation. As Dr. Smith said previously, we look at these drugs in a larger context with others in-class and limit resources -- the most valuable which is the clinical trial eligible patient -- in a step-wise way, and move to subsequent steps when we cross specific thresholds. I think painting that global picture for a target for a drug is particularly challenging when the drugs are reviewed individually. Thank you.

DR. PAPPO: Thank you.

Dr. Smith?

DR. SMITH: Yes. Malcolm Smith, NCI. In terms of the new drugs and biological products, I wanted to make one comment about a specific class

of agents, and those are the antibody drug conjugates, or ADCs, that I think are going to be really important -- they already are -- for cancer like Hodgkin lymphoma and inotuzumab ozogamicin for ALL, but I think they'll be very important in the coming years. My perspective on how to dose these types of agents is informed by the writings of Jon Lambert, so it's on me if I misinterpret some of the things he said. But he makes a point that mice and humans have about the same plasma per kilogram of body weight, so with a few assumptions, you can extrapolate or approximate the activity in mice and humans at a particular dose. They should be relatively equal.

When you look at ADCs, and I'll focus on the maytansinoids, they're usually in the mice and have activity in the 3 to 4 milligram-per-kilogram range, but with the activity increasing and the regression becoming much more robust -- up to 10 or 15 milligram per kilogram, and in humans, the trastuzumab emtansine -- the MTD was 3.6 milligram per kilogram, so that one would predict that if you

were able, if there weren't any of the toxicities associated with the agent and you could get the higher doses, you would be able to have better responses.

We saw this with glembatumumab vedotin, where we could only give 1.9 milligram per kilogram per dose every 21 days, an in the preclinical setting, really, minimal activity was seen at a higher dose, 2.5 milligram per kilogram given every 4 days. And then finally, even with the topo1 payloads, which are dosed in the clinic, an example was given where the dose was between 5 and 6 milligrams per kilogram, but the preclinical doses, you see dose response up to doses of at least 10 milligram per kilogram, and perhaps higher.

So as we move these agents into testing in children, I think unless there's really good PK or PD modeling data that shows that there may not be a dose-response effect over the ADC doses that we plan to use in children, then we really should be using doses that are tolerable, and basing our

experience on the tolerable doses in adults and not worrying that we have to go through extensive dose optimization for this class of agents. That's all. Thank you.

DR. PAPPO: Thank you very much, Malcolm.

Dr. Balis?

DR. BALIS: Thank you, Dr. Pappo. This is Frank Balis. I think that the drugs that we're looking at now, as I mentioned, are more like classical agents that we think about when we think about pharmacology, and that is that they bind receptors. And there, dose response curve oftentimes looks like the curve that Dr. Wessel showed early in her talk that at some point reaches a maximal effect. And once you've reached that maximal effect, increasing the dose is not going to substantially increase the therapeutic effect of the drug. The problem that we have and the way to define an optimal dose is to actually characterize the dose-response curve. Unfortunately, when we do dose escalation studies in kids, we started a dose that's already pretty close to the maximal effect,

presumably, if that was reached in adults, and we do very small incremental dose escalation.

As an example, to get from an IC50 concentration to an IC90 concentration for most agents is a 10-fold increase in the concentration and we, of course, never do dose escalations that are anywhere close to that in terms of the range that we look at, and that only defines half of the dose-response curve.

So the limitation here is that we can't go back and do very low doses that are potentially non-therapeutic in kids as a way to better define the dose-response curve for the tumors that occur in them in pediatric populations. The only really way around it, and the way that studies with non-cancer drugs used to be done many years ago, is using intra-patient dose escalations. Again, that would be potentially feasible if we had a short-term endpoint that we could measure to look at effect, and then quickly get the patients escalated up to a dose that we think is closer to a therapeutic range. But from the perspective of

classical pharmacology, we really aren't achieving the goal, particularly about defining or characterizing a dose-response curve as a way to select the optimal dose of the drug to use. Thanks.

DR. PAPPO: Thank you very much.

Any additional comments on the second question?

(No response.)

DR. PAPPO: So if I can briefly summarize this, apparently postmarketing studies are going to be important in discussing the potential challenges to identify dosage for new drugs and biological products in patients and FDA-approved drugs. Funding might be an issue in specific clinical trials. We need to pay special attention to a class of drugs which are antibody drug conjugates, in which dose escalation might actually be of importance in selected cases given higher doses, and PK and PD may not adequately represent the actual dose of the response that we're looking for. We also need to characterize dose-response curves a

little bit better and consideration of intra-patient dose escalation as a short-term endpoint in some of these studies.

I hope that I summarized all of your thoughts or, Malcolm, anything else to add?

DR. SMITH: Yes. In terms of my comments, the point was that for antibody drug conjugates and studying them in children, I think the question really is, are we at the top of the dose-response curve and on the plateau, or are we still in the rising slope of the dose-response curve? I think for most antibody drug conjugates, or absent additional PK/PD modeling data that a company may have that we are on the plateau, I think the assumption is that we're probably even at the tolerable doses in humans on that part of the dose-response that's still increasing.

So dose optimization at that point, other than making sure that the dose is tolerable in children, we don't want to have too much interstitial lung disease, or too much parotitis, or some other ADC effect, but absent additional

data, I think it's likely that the ADCs will be on the increasing slope of the dose-response curve at the doses that are tolerable in humans and children.

DR. PAPPO: Thank you for the clarification.

Dr. Glade Bender?

DR. GLADE BENDER: I just wanted to add one more comment to my points about postmarketing studies as well. I think they may be a good strategy for industry and for the patient. I think the burden of those strategies is actually on academia because these studies are considered not as scientifically interesting at the institutional level, but obviously critically important to the patients and the development of the drug. So for those postmarketing studies, I think somehow the challenge will be to make them appealing to academia because they carry with them the same infrastructure and resource cost as some of the earlier and more exciting studies.

DR. PAPPO: Thank you for your comment.

Any additional suggestions or comments on

question number 2?

(No response.)

DR. PAPPO: If not, we're going to move to question number 3. For drugs and biological products being developed in both adult and pediatric patients with cancer, consider how the timing of dosage selection in adults impacts the timing of trial initiation and dosage optimization in pediatric patients with cancer.

If there are no questions or comments regarding the wording of the question, we will now open this question for discussion, and we will start with Dr. Steve DuBois.

DR. DuBOIS: Thanks, Dr. Pappo. Steve DuBois, Dana-Farber/Boston Children's. I'm pleased to see that nearly everyone, I think, has said that we don't need to wait for a final, optimized, adult dose before we can embark on pediatric development, and I certainly echo that. From my standpoint, I think we have an ethical obligation to a minor participant that there be some potential prospect for benefit. I always feel better working with a

dose that is a starting dose for a first-in-child study that has some prospect of benefit, and that this is not like a homeopathic dose of the medication. But barring that, if we think that there's a prospect for benefit, I think it's reasonable to proceed.

I think as well, sometimes, because of the nature of the patients who are coming to first-in-child clinical trials and their extent and type of pretreatment, we sometimes see different toxicity profiles. So I think we can't always be totally reassured by what we see in the adult experience. For example, our patients receive, at least in the solid tumor world, much more intensive alkylator pretreatment, and we've seen more hematologic toxicity with some novel agents maybe than we might have predicted from the adult experience. Thank you.

DR. PAPPO: And to your point as far as delaying the impact of these drugs in pediatrics, even in the trials that you published in your paper with a delay of 6-and-a-half years, a lot of those

studies did not even include dose optimization in adults. So there's a big delay, and we need to try to optimize this and get those drugs faster in children.

DR. DuBOIS: Yes. I totally agree.

DR. PAPPO: Do we have any additional comments?

Dr. Laetsch?

DR. LAETSCH: I would just second what Dr. DuBois said. I agree completely that early initiation of pediatric clinical trials is important, and just highlight again what I said in response to question 1 around designing initial trials to evaluate the dose in a relatively small number of patients and get some hint of activity before proceeding with large pediatric dose optimization studies, which may come later and may borrow and extrapolate data from adult dose optimization trials.

DR. PAPPO: Thank you.

Dr. Yoram Unguru?

DR. UNGURU: Thank you, Dr. Pappo. Yoram

Unguru from Children's Hospital of Sinai and Johns Hopkins Berman Institute of Bioethics. I want to dovetail on something that Dr. DuBois said that I think is really apt.

In ethics, we oftentimes think about treating similar people similarly, similar research participants similarly, similar cases similarly, and if we're thinking about how to optimize trials for dose optimization and relating kids to adults, a corollary might be thinking of a traditional phase 1 trial or an early-phase trial where a question oftentimes, at least ethically, is raised, "Should we limit participation to patients who've only exhausted other alternatives?"

There's an ethical argument that's made that you don't need to take that tact so long as -- and this goes to his point -- there is a prospect of some benefit that the risk is not too toxic and that the risks can be justified based upon anticipated benefits to participants, specifically as it relates to available alternatives.

I think there's something to be said there.

I do think that this would require a bit of a frameshift in how these trials are broached and discussed with our patients and our patients' families. I think a lot of the heavy lifting is important in that space.

DR. PAPPO: Thank you very much.

Any additional comments? Dr. Frank Balis?

DR. BALIS: Thank you, Dr. Pappo. This is Frank Balis. I think that one of the changes that occurred moving from cytotoxic drugs to targeted agents is that we weren't really too concerned about the mechanisms or the scientific rationale necessarily for moving cytotoxic drugs into pediatrics just because, in many cases, in general, cytotoxic agents tend to be more active in childhood cancers, so we moved them along without thinking much about that.

I think now we can spend a lot more time prioritizing drugs based on the target of the agent and whether that target is expressed, or the antigen is expressed, in childhood cancers, specific cancers, and obviously ones with a greater

scientific rationale could probably take precedence in terms of moving ahead earlier in development, as opposed to those where we may not have a strong scientific rationale for studying them in childhood cancers, despite the fact that we do or don't have activity data in adults. Thanks.

DR. PAPPO: Dr. Glade Bender?

DR. GLADE BENDER: Julia Glade Bender from Memorial Sloan Kettering. I think, again, the point that we had made about targeting pharmacokinetic endpoints and the need to understand dose response, the adult data really helps there, whereas there are some pediatric diseases for which the dose exposure may need to be higher, like the example of crizotinib in neuroblastoma, for the most part -- it doesn't need to be lower -- at least at first to see whether or not there is a signal of efficacy.

So I think if the dose-response relationship is actually seen and known in adults, that is very helpful to anchor a pediatric trial, where if we get some early real-time PK and know that we are

below that threshold, that we should advance quickly through our dose escalation, and then work on the optimization.

DR. PAPPO: Thank you very much.

Any additional comments on this question?

(No response.)

DR. PAPPO: So I think that the overall consensus was not to wait for final adult optimization studies to start pediatric studies; that there's an ethical obligation for us to move forward with drugs that could potentially offer a prospect of benefit, and we need to take into consideration that the toxicity profile that is seen in adults might be slightly different in pediatrics.

It's important to have early initiation of pediatric clinical trials and designing small clinical trials perhaps mostly based on the data from adults with dose-response relationships seen in adults. And then once we identify a potential target or potential benefit, then you can proceed with dose optimization studies. We also need to

reconsider how we approach families for these phase 1 studies and how we select the populations for these studies.

Did I get the gist of it? Did I miss anything? Do you want to add anything?

(No response.)

DR. PAPPO: Okay.

So now we will move to question number 4, and this is, discuss the considerations for dosage optimization in pediatric oncology clinical trials investigating combination therapies.

If there are no questions or comments concerning the wording of this question, we will now open this question for discussion, and we're going to start with Dr. Steve DuBois.

DR. DuBOIS: Thanks, Dr. Pappo. Steve DuBois, Dana-Farber/Boston Children's. I think it's important just to say here that this should be not just dose optimization, but dose and schedule optimization. We've seen now several examples in the pediatric oncology clinic in which, for example, anti-androgenic TKIs have not been

tolerable along with concomitant conventional cytotoxic chemotherapy, but have been tolerable with sequential dosing; so I think keeping in mind not just dose optimization but schedule optimization.

DR. PAPPO: Thank you very much.

Dr. Malcolm Smith?

DR. SMITH: Yes. Malcolm Smith, NCI. The point I want to make is one that Dr. DuBois made earlier, that combination therapy really is central to what we do in pediatric cancer, and to all of our curative therapies, going back all the way to Frei and Freireich, our progress in ALL, and all the other cancers that we've had effective therapies for, has occurred when we've taken agents that have single-agent activity and have combined these with other active agents, and then have conducted sequential clinical trials to determine how best to dose-sequence schedule these agents.

I think the one issue with how we do this is when you add a new agent to an existing combination -- if that's what you're doing, and

it's the most common thing -- if you do have to reduce one of the standard-of-care agents, this decreases your chances of success. It doesn't mean you won't be successful, but then you have to not only bring new activity, but you have to make up for the activity lost by that standard agent.

So the ideal combinations are those when we have the agent that we're bringing in, and we can use it at its effective dose as a single agent and can combine it directly with the regimen that we want to at its standard doses. Rituximab added to CHOP is the classic example of that working very well. So that's just one point about how when we create these combinations, one thing to consider. Thank you.

DR. PAPPO: Not overlapping toxicities, right? That's the other point.

DR. SMITH: Yes. Generally, if they're non-overlapping toxicities, if you have a myelotoxic agent, you're probably not going to be able to add it to ifos, etopocide, or VAC, but it's possible that if it's another non-heme toxicity,

well, that's exactly right, non-overlapping toxicities. It will allow you to add doses, full [indiscernible] doses of all the agents.

DR. PAPPO: Then just to expand a little bit on what you were saying, Malcolm, as far as activities of agents, we are also pursuing combinations even when there is lack of activity. For example, checkpoint inhibitors in pediatrics, now we're combining them with TKIs. I guess that is just basically following what the adults are doing, even though there's really not a whole lot of evidence that checkpoint inhibitors have a big role in the vast majority of pediatric solid tumors.

DR. SMITH: Yes. Those, of course, are experimental trials. The success in adding agents that don't have single-agent activity to existing combinations, or to active agents, or active combinations has been limited, very limited. So I think, by far, our greatest chance of success is when we can take an agent that does have single-agent activity for the disease we're

treating and combine it with other agents with single-agent activity.

DR. PAPPO: Thank you, Dr. Smith.

Dr. Glade Bender?

DR. GLADE BENDER: Julia Glade Bender, Memorial Sloan Kettering. I just want to revisit a point that's been made by many people here, which is really that I think combinations is where we go, but we generally think of the single-agent phase 1 trial as the time when you get your PK, and then when you get to a combination study, unless there is a rationale that there may be drug-drug, interaction, the PK becomes less important and/or is difficult to fund, and people are not interested in collecting PK.

But I think this is a wonderful opportunity to optimize individual drug doses when one gives them in combination, as was the case in the randomized trial that Dr. Wessel presented at the beginning, where you're looking at both important efficacy, i.e., drugs in combination that are more likely to be effective in children than single

agents, and hopefully patients that will be on for a longer period of time.

So my plea is that we actually do more PK on our combination therapy trials so that we can optimize new agents in the context where we actually plan to give them and for longer periods of time. I think this is an underutilized opportunity in our current drug development pathway.

DR. PAPPO: Thank you.

Jonathan?

DR. CHENG: Hi. Jon Chen, industry rep. I appreciate the discussion, and I guess I just want to provide the perspective that combination therapy, of course, is what we want to do once we understand the single-agent aspect, including the dose optimization. However, oftentimes for a drug development process, we want it to combine with many, many agents, and I do think it sometimes can be a challenge to dose optimize for each single combination.

So I wonder if "dose optimization" is the

right word, particularly in a program where you're combining across many indications, across many lines of therapy, and across many combinations, because I would hope that if the dose optimization is done -- and I appreciate the importance of that -- and there isn't drug-drug interaction, and the combination is tolerable, I'm not sure that optimization is always as critical the question. Oftentimes, you're just looking for the ability to combine at full doses. And I think that if one were to need to dose optimize, particularly in a randomized setting, for each combination, that is oftentimes quite an investment of resources, and oftentimes that might take away from other opportunities.

So I just wanted to provide that perspective. I do appreciate the importance of dose optimization, but when you get to combination therapy, particularly the multiplicity nature of how many combinations one often wants to provide, as well as across many indications, optimization might be difficult for every single one of those.

DR. PAPPO: Thank you very much.

Steve?

DR. DuBOIS: Thanks so much. I wanted to pick up on something that Dr. Glade Bender said, and it's a little bit of an advertisement for a poster we presented at JCO and a little bit of a cautionary tale for people who publish phase 1 clinical trials.

We completed an analysis of all of the phase 1 trials published in JCO over a 20-year period, and we're interested to look at the toxicity reporting, not the granular toxicities but where cycle 2 and later DLTs reported, where dose modifications reported, and we were pretty shocked to find that the reporting, once you get past cycle 1, is pretty poor.

So specifically, only 9.6 percent of the papers reported whether there were dose-limiting toxicities in subsequent cycles and only 19 percent reported whether there were dose modifications beyond the first cycle. I think we're all end users of those papers, and I think important,

particularly to Julia's point, is that patients are often on these, particularly, combination trials for longer periods of time, and it's helpful to understand what the cumulative exposure or the cumulative likelihood of significant toxicity is for these patients.

DR. PAPPO: Thank you very much.

Any additional comments or questions?

(No response.)

DR. PAPPO: I will try to summarize this discussion on this final question. We need to take into consideration when we're combining new agents not only dose optimization but also schedule optimization. There are several examples showing the sequential dose, and sometimes it's possible when you combine two agents, whereas when you do it together, you cannot do this combo together.

We also need to understand that when we put together the no-agent combinations, that we do not limit the efficacy or perhaps the combination that is active against this disease; so try to be sure that we optimize the combinations and look for

non-overlapping toxicities to try to maximize the success of the trial. PK and phase combination trials may also be important to optimize some of these studies, so not only PK in the phase 1 but also the time that you're doing the combination trial. It is also important to define really what dose optimization is in selected patients and the opportunity to combine these agents to try to maximize the activity. So whether "optimization" is the right word is unclear.

Then the final comment was that some of these patients, when you use a targeted agent, for example, with combination chemotherapy, they might be on it for a significant amount of time, so we also need to be aware of the fact that there can be other toxicities that are not reported after the first cycle, and we need to keep an eye on the cumulative likelihood of toxicities in this subset of patients.

Did I miss anything or does anybody want to add anything to question number 4?

(No response.)

DR. PAPPO: Okay.

So we will now proceed with the FDA closing remarks from Dr. Martha Donoghue.

Closing Remarks - Martha Donoghue

DR. DONOGHUE: Thank you, Dr. Pappo.

I first just wanted to thank all of you who participated in today's discussion, as well as those of you online who are listening to us today. I think we had a really robust discussion on dosage optimization in pediatric oncology, and it was exactly what we were hoping to achieve, namely to gain a better understanding of each other's perspectives and to set the stage for further work together.

Two things that struck me as I was listening to today's discussions, the first one being that I think we as a community have many areas in which we agree with respect to dosage optimization in oncology for pediatric patients with cancer. Recurring themes include that early initiation of clinical trials of drugs that hold promise for pediatric cancers in pediatric patients is very

important and shouldn't wait until the dosage is optimized in adults.

What is important in terms of timing is that we have a degree of assurance that there's a prospect of clinical benefit in pediatric patients, and it's preferred to have the information that we need, if possible, to identify the starting dose that will be therapeutic, potentially, in pediatric patients in order to provide that prospect of direct clinical benefit.

I think we also agree as a community that optimizing the dosages of new cancer drugs to treat pediatric patients is important, and that there's a need to be thoughtful in our approach to dosage optimization during the drug development continuum due to the scarcity of patients, patient resources, financial resources, and other resources, including time and the need to promote drug development that is efficient as possible.

I heard a lot about the importance of pediatric appropriate strengths and dosage forms because they're important for our orally

administered drugs, in particular, to precisely deliver the intended dosages we are studying. For those drugs where there's a strong signal or overwhelmingly strong biological rationale, we should work toward having a pediatric and age-appropriate formulation as soon as possible.

Lastly, decisions with respect to dosage optimization shouldn't be made in a vacuum. We should leverage our collective experience, including preclinical data and clinical experience in adults; experience with similar drugs in-class, PK/PD data, et cetera, and we should work together as a community to align as much as possible in our decision making, and ongoing communication amongst all stakeholders is essential.

And my last impression is that we all have continued work to do as a community in order to optimize our approach to dosage optimization. As Dr. Balis mentioned during part of the discussion, we need better endpoints, and it was reminded that as science and techniques evolve -- including identification of better biomarkers that are

preclinical models, increased use of therapeutic drug monitoring, et cetera -- our strategy for dosage optimization should also evolve.

Lastly, this is obviously a very complicated topic and that decisions will be made often on a case-by-case basis. At the risk of repeating myself again, I think continued work and ongoing multistakeholder communication and collaboration is needed; so we all should commit to continued work together as we move forward. And as always, please feel free to reach out to me or others at FDA if you have additional thinking that you think is important to convey to us as we go about our work, thought for continued engagement, et cetera, because we are eager to continue this work. So thank you again for your attention and time.

Adjournment

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

I just want to thank Gretchen, Joseph, and Takyiah for their support and for making this meeting possible, and I want to thank all of you

for attending, and hopefully we'll see each other next year. We will now adjourn the meeting, and thank you very much.

(Whereupon, at 2:50 p.m., the meeting was adjourned.)