FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

Topic 1

Thursday, June 22, 2017

8:00 a.m. to 10:03 a.m.

FDA White Oak Campus

The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Lauren Tesh, PharmD, BCPS

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Alberto S. Pappo, MD

(Chairperson, pedsODAC)

Member and Head, Division of Solid Malignancies

St Jude Children's Research Hospital

Professor of Pediatrics

University of Tennessee Health Science Center

Memphis, Tennessee

Courtney J. Preusse, MA

(Consumer Representative)

Senior Research Administrator and CLIA Operations Director

Fred Hutchinson Cancer Research Center

Seattle, Washington

Bruce J. Roth, MD

Department of Internal Medicine

Division of Medical Oncology

St. Louis, Missouri

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS

(Non-Voting)

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

(Industry Representative)

Executive Medical Director, Amgen Oncology

Therapeutic Area Head, US Medical Organization

One Amgen Center Drive

Thousand Oaks, California

TEMPORARY MEMBERS (Voting)

Anne L. Angiolillo, MD

(Participation in Day 1, Topic 3, Participation in Day 2)

Director, Leukemia & Lymphoma Program
Division of Oncology
Center for Cancer and Blood Disorders
Children's National Medical Center
Professor of Pediatrics
The George Washington University School of Medicine and Health Sciences
Washington, District of Columbia

Carola A. S. Arndt, MD

Professor of Pediatrics and Consultant
Division of Pediatric Hematology/Oncology
Department of Pediatric and Adolescent Medicine
Mayo Clinic College of Medicine and Science
Rochester, Minnesota

Richard G. Gorlick, MD

Division Head and Chair, Pediatrics

Robert A. Mosbacher Chair of Pediatrics

The University of Texas MD Anderson

Children's Cancer Hospital

Houston, Texas

Leo Mascarenhas, MD, MS

Deputy Director

Children's Center for Cancer and Blood Diseases

Section Head – Oncology, Associate Professor of Pediatrics

Division of Hematology, Oncology, and Blood and Marrow Transplantation

Children's Hospital Los Angeles

Keck School of Medicine, University of Southern California

Los Angeles, California

Elizabeth A. Raetz, MD
Professor of Pediatrics
Medical Director, Leukemia and Lymphoma Program
Pediatric Hematology/Oncology
University of Utah
Huntsman Cancer Institute
Primary Children's Hospital
Salt Lake City, Utah

Brenda J. Weigel, MD, MSc
Professor
Division Director, Pediatric Hematology/Oncology
University of Minnesota
Developmental Therapeutics Chair
Children's Oncology Group
Minneapolis, Minnesota

FDA PARTICIPANTS (Non-Voting)

Gregory Reaman, MD

Associate Office Director

Associate Director for Pediatric Oncology

Oncology Center of Excellence

Office of Hematology and Oncology

Products (OHOP)

Office of New Drugs (OND), CDER, FDA

Leslie Doros, MD

(Participation in Day 2, Topic 1)

Medical Officer

DOP2, OHOP, OND, CDER, FDA

C O N T E N T S

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

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

I would now like for all the members, consultants, FDA panel, and DFO to go around the table and state their name for the record.

DR. MORROW: P.K. Morrow, medical oncologist, employed by Amgen.

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

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

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

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

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

DR. PAPPO: Alberto Pappo, pediatric oncology, St. Jude Children's Hospital in Memphis and chairperson of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee.

DR. TESH: Lauren Tesh, designated federal officer.

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

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

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

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

DR. DOROS: Leslie Doros, medical officer, FDA.

DR. REAMAN: Gregory Reaman, FDA.

DR. PAPPO: We will now proceed with opening remarks from Dr. Greg Reaman.

FDA Introductory Remarks

DR. REAMAN: I just welcome our advisors back for day 2 of this meeting, which, again as I explained yesterday, is really envisioned as an opportunity for an interactive discussion between advisors, industry, and the agency to gauge the level of interest and to evaluate any existing evidence on perhaps developing specific products for pediatric oncology indications.

We're doing this to really maximize our authority under the Best Pharmaceuticals for Children Act since the mandate provided by the Pediatric Research Equity Act really doesn't pertain to oncology drugs. And we are trying to issue written requests, when appropriate, as early as possible rather than waiting until years after a product is approved to begin pediatric investigations.

So these are commitments between the agency

and sponsors to develop drugs along the lines of specifically outlined protocols. The agreements can be amended should preliminary studies demonstrate that there's no reason to further develop a specific product, and we feel that these early discussions have enabled us to, number one, issue more written requests and to issue them much earlier in a product's development timeline.

So I'd like to also acknowledge Eli Lilly for accepting our invitation to discuss two potentially relevant and interesting products this morning. Thanks.

DR. PAPPO: Thank you, Dr. Reaman.

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

look forward to a productive meeting.

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

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

We will now proceed with topic number 1, olaratumab from Eli Lilly and Company. Dr. Lauren Tesh will read the conflict of interest statement for this session.

Conflict of Interest Statement

DR. TESH: The Food and Drug Administration is convening today's meeting of the pediatric subcommittee of the Oncologic Drugs Advisory

Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her

potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of the committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

This session's agenda involves information to gauge investigator interest in exploring potential pediatric development plans for two products in various stages of development for adult cancer indications. The subcommittee will consider and discuss issues concerning diseases to be

studied, patient populations to be included, and possible study designs of the development of these products for pediatric use. The discussion will also provide information to the agency pertinent to the formulation of written request for pediatric studies if appropriate.

The product under consideration for this session is olaratumab, presentation by Eli Lilly and Company. This is a particular matters meeting during which specific matters related to Eli Lilly and Company's product will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Drs. Carola Arndt, Leo Mascarenhas, Alberto Pappo, and Brenda Weigel.

Dr. Arndt's waiver involves her stock holdings in two potentially competing firms. Dr. Mascarenhas's waiver involves his employer's current study of olaratumab, funded by Eli Lilly, which is anticipated to be between $100,001 and

$300,000 in total funding. Dr. Pappo's waiver involves his employer's current study of olaratumab funded by Eli Lilly, which is anticipated to be $50,001 and $100,000 per year. Dr. Weigel's waiver involves her employer's current study of olaratumab, funded by Eli Lilly, which are anticipated to be between $0 and $50,000 in total funding.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on the FDA's website. Copies of the waivers may also be obtained by submitting written requests to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland 20857 or requests may be sent via fax to (301) 827-9267.

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

With respect to FDA's invited industry

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

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

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

DR. PAPPO: Thank you, Dr. Tesh.

Both the Food and Drug Administration and the public believe in a transparent process for

information-gathering and decision-making. To ensure such transparency of the advisory committee meeting, the FDA believes it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based upon the outcome of the meeting.

Likewise, the FDA encourages you, at the beginning of your 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 presentation, it will not preclude you from speaking. We will now proceed with Eli Lilly's presentation.

Industry Presentation - Allen Melemed

DR. MELEMED: I'd first like to thank FDA for the opportunity to present to the pediatric ODAC today. My name is Allen Melemed. I'm a pediatric oncologist, and I currently am responsible for the U.S. regulatory for Eli Lilly Oncology.

We're delighted to be here today to discuss two of our compounds, the first one being olaratumab and the second one being prexasertib, and we are really looking forward to get your advice on how best to develop these medications for childhood cancers. I'm going to talk first for the first couple slides, and then following me Dr. Wacheck, and he'll give the explanation regarding olaratumab with pediatric and adult development.

When you look at our development scheme at Lilly, we really look at it as a bench to the bedside approach. And our first area is, we try to build internally non-clinical models that we can study our compounds first. When we see activity, we then can expand them into other models, into

in vivo models and try to really understand the best places to go. And then we support that into the clinical trials that we're going to move.

Dr. Wacheck is going to tell some of the data that we have and some of the reasons why we're excited to look into osteosarcoma for olaratumab, but we're open to get feedback from the committee if there are other areas we should be looking at, too. The obvious goal here is to improve treatment options for children with cancer, and today and right now, we're presenting olaratumab.

I want to get to some background for people who are not familiar with pediatric cancers. For a lot of the members, this should be second nature. But in general, enrollment to pediatric cancers are rare tumors, and they're complex. Many kids' cancers are treated with multiple therapies, which would include chemotherapy, radiation therapy, surgery, often a combination of all of them. So the isolation of a single drug can be complicated. It's also a challenge because most of these regimens are given as combinations. Again, trying

to isolate the single effect on one drug can be a challenge.

As I mentioned before, the translation to the non-clinical models into the clinic have not been 100 percent effective, and that's a challenge. And the risk-benefit is something we always have to think about. If we're trying to really cure a childhood cancer, long-term side effects is a challenge for these unlucky patients.

I'm going to now have Dr. Wacheck come discuss the olaratumab development plan for both pediatrics and adults.

Industry Presentation - Volker Wacheck

DR. WACHECK: Thank you, Dr. Melemed.

My name is Volker Wacheck, and I have the pleasure to support olaratumab as the medical director. And over the next 20 minutes, what I would like to do is to share with you my enthusiasm for this molecule. To do so, I would like to give you a brief overview about the compound and the mechanism of action, speak a little bit about the regulatory history, and then get into the clinical

trial experience with adults, which greatly informed us in the design of the early study in pediatric indication as well as moving further on, and then speak in particular about the non-clinical, and that there are ongoing studies, and then to conclude with next steps in the pediatric development.

As an executive summary, let me start that the excitement for this molecule is based on the substantial improvement that we have observed in the combination with doxorubicin in the treatment of soft-tissue sarcoma patients that led to a significant increase in the overall survival in this population without an increase in significant toxicity.

We closely collaborated with the FDA after having that data to get this compound to patients in extensive regulatory interaction, which led to the accelerated approval of olaratumab by the end of last year. Now we are committed to bring this compound also to the pediatric patient population, particularly considering that the relative

frequency of sarcoma is higher in that pediatric population. And to that end, we have initiated a phase 1 study looking at the monotherapy as well as combination treatment of olaratumab with standard-of-care treatment.

Lastly, we think that the non-clinical as well as the clinical data that we have in hand provide a rationale to further study olaratumab in pediatric indications; and particularly the data here in osteosarcoma and rhabdomyosarcoma are of interest to further being evaluated.

I would like to start with an overview of the compound that we are talking about and introducing the pathway. So the platelet-derived growth factor receptors are a transmembrane tyrosine kinase receptor. There are two different forms, an alpha and a beta form. What we know is that there are four different ligands expressed by four different genes. And upon binding of the ligand to the receptor, what happens is there's a dimerization of the receptor that leads to the phosphorylation of the intracellular kinase domain

of the PDGF receptor.

It then triggers a couple of pleiotropic downstream signaling pathway that, in one or the other way, are related to the differentiation of mesenchymal cells in particular, stem cell differentiation, but also have links to the promotion of growth of tumor, angiogenesis, migration, and wound shielding.

The role or the presence of the PDGF receptor family, in particular alpha, is something that is already known for decades. Looking back, we know that, in sarcomas, about 8 to 50 percent, depending on the assay and the kind of use, do express the PDGF receptor alpha. And this expression has been linked with a more aggressive phenotype and an increased metastatic potential.

The PDGF receptor alpha is not only expressed on the tumor. We know also that in the microenvironment, in the cancer-associated fibroblast around the tumor, there is expression of the receptor and there is a fascinating crosstalk between the microenvironment and the tumor around

this pathway with paracline as well as autocrine loops, each other are promoting here the different facts for PDGF receptor signaling.

The molecule that we have is olaratumab. It's a fully human monoclonal antibody, IgG1, directed against the PDGF receptor alpha. And upon binding with high affinity, what it does is it blocks the binding of PDGF AA, PDGF BB, and CC. By doing so, it inhibits the phosphorylation of the intracellular kinase domain and the further ligand-dependent signaling downstream of the receptor.

To illustrate how we accelerated the development for this molecule, I would like to briefly touch on the regulatory history. Olaratumab, or Lartruvo as the trade name, has received accelerated approval in October 2016. And this platelet-derived growth factor receptor alpha blocking antibody, is indicated in combination with doxorubicin for treatment of adult patients with soft tissue sarcoma with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative

treatment with radiotherapy or surgery.

The dose that is approved for Lartruvo is 15 milligram per kilogram, administered as an infusion on day 1 and to day 8 of a 21-day cycle in combination with a standard dose of doxorubicin.

This slide illustrates the extensive as well as intensive collaboration that we had with the agency to bring the molecule to the market. As soon as we have seen early in 2014 the first interim results, we get into discussion and conversation with the agency that led to a breakthrough designation and finally led to the accelerated approval by October of last year for this compound.

But at the same time -- and that is seen here underneath the timeline -- we already initiated and thought about in terms of the further pediatric development of the molecule and submitted our phase 1 protocol to the IND, received feedback from the agency, incorporated that, and had the first patient visit in this pediatric study by August of 2016.

A lot of thoughts and consideration went into the design of this phase 1 study, but also for the overall strategy, is based on our observation that we had in the adult soft tissue sarcoma. So I would briefly like to review these data.

The development for olaratumab started in 2006 with a standard phase 1 study looking at the monotherapy, different dose level from 4 up to 20 milligrams per kilogram. And in this dose-escalation study, we didn't observe the dose-limiting toxicity. The most frequent adverse events were rather unspecific, with fatigue, some GI toxicity, but all of them grade 1 or grade 2.

Pharmacokinetics supported for the development in that we saw a dose-dependent increase that was compatible with the target-mediated drug disposition model.

In terms of the recommended phase 2 dose, the dose of 50 milligrams per kilogram given on day 1 and day 8 was selected based on the notion that in pre-clinical animal models, we have seen trough levels that were associated with activity at this

50 milligram-per kilogram dose level.

In the meantime, there are a total of 15 trials that have been or are ongoing with olaratumab, most of them in combination with chemotherapeutic regimens and the majority, 7, in soft tissue sarcoma, including one trial, a phase 3 trial, whereas the other ones are all either phase 1 or phase 2. But we also looked in combination with chemotherapy in non-soft tissue sarcoma indication, so ovarian, lung, pancreas, and prostate, as well as for the monotherapy of this particular molecule.

The most relevant studies so far for olaratumab is the phase 2 study that led to the accelerated approval. This study was an open-label multi-center phase 1/2 study consisting of two parts. The first was a 1b part where we assessed, in patients with advanced soft tissue sarcoma not amenable to surgery or radiotherapy, older than the age of 18, and any number of prior treatments, but no doxorubicin, the safety and tolerability of combining the olaratumab with the doxorubicin.

Patients that didn't progress at the end of treatment were allowed to continue olaratumab as a monotherapy.

After having established in this lead in the safety of that combination, we moved on to randomized phase 2 study with exactly the same patient population here and randomized 130 patients to the two treatment arms in a 1 to 1 ratio either for the combination of olaratumab and doxorubicin or to doxorubicin as a monotherapy. Again, patients were allowed to continue if not progressing at the end of 8 cycles of treatment with doxorubicin.

This trial was stratified for common prognostic factors, including ECOG status, the number of prior lines of therapy, histology, as well as we did a stratification according to the PDGF receptor alpha expression status.

The primary objective of that study was progression-free survival, and the study met its pre-defined target for progression-free survival. Then we observed in the combination arm the 2.5

months' improvement in progression-free survival, which meant the pre-defined criteria, acceptance level of 0.2, an alpha level in that study.

Importantly, there was an open-label study here that was an independent review of the CT scan to re-assess the PFS here. And the hazard ratio that we observed for the investigator-based assessment of 0.67 was confirmed by this independent review, almost with the identical number in terms of the hazard ratio.

As a key secondary objective to that study, we also looked for overall survival. And there we observed a statistically significant and clinically meaningful improvement.

Relative to the 14.7 months overall survival in the control arm, which is in line with previous study for doxorubicin here in the monotherapy, we observed an 11.8-month improvement by the addition of the olaratumab that resides within 26.5 months of overall survival and a hazard ratio of 0.46.

This result was highly statistically significant. The Kaplan-Meier curve separated

early on and stayed separated. And to the best of our knowledge, it's the first time that in a randomized study in that setting, the median overall survival exceeded the two-year landmark in soft tissue sarcoma.

The safety profile for the combination of olaratumab and doxorubicin in this study was acceptable, and the adverse events that have been seen were monitorable and manageable. Overall, there was a slightly higher number of adverse events in the combination arm for known toxicities that have been described as doxorubicin like nausea, mucositis, vomiting, and diarrhea, but most of them were either grade 1 or grade 2.

There was also a higher grade of neutropenia observed in the combination arm that included also a higher rate of grade 3 or more events. But that didn't lead [indiscernible] into an increased number of febrile neutropenia, which was almost the same between the two arms. And also, this neutropenia did not lead to a higher rate of discontinuation, hospitalizations, or death in that

study.

As an antibody, there are certainly adverse events of special interest, particularly about immunogenicity, and we observed in 12.5 percent here infusion-related reactions. Typically, these were seen within the first two cycles of therapy, and there were 2 patients or 3.1 percent actually with high grade that were seen after the first infusion of olaratumab.

The cardiotoxicity as a well-known characteristic of doxorubicin side effects was similar between the two treatment arms with no hint that the addition of olaratumab increased any cardiotoxicity.

From a PK perspective, olaratumab behaved as we would have expected here for a monoclonal antibody. For the analysis, we did a PopPK study with a total of 171 patients, samples that were pooled from different phase 2 studies. And the characteristics of the antibody are best described by a two-compartment model with linear elimination at the 15- and 20-milligram per-kilogram dose

level. The half-life of the molecule is around 11 days, and steady-state conditions are obtained after about 50 day equal to about cycle 3.

Further, looking into the data, we valued it whether any covariates, demographic baseline factors might influence here the PK characteristic. And the most notable that we observed is that the clearance decreased with decreasing body weight in a less than directly proportional manner, as well as that co-administration of olaratumab didn't influence the PK characteristic of doxorubicin and vice versa.

The exposure response relationship indicated that the majority of patients are above the half-maximal effect and receiving overall survival benefit. So in the survival model, where we use the trough level at the end of cycle 1 and OS as in time to event analysis, there was the half-maximum effect seen at 66 micrograms per milliliter, which corresponded to the 25th percentile in that study population.

Maximum predicted effect in terms of overall

survival was seen with an approximate 75 percent improvement, and that was within the dose level that were achieved within that study for olaratumab.

In terms of significant covariates in that model, the only that were identified were the ECOG performance status as well as previous lines of chemotherapy that are a well-known prognostic factor in that patient population.

So overall, the benefit-risk balance for olaratumab in combination with doxorubicin is a positive. The efficacy results represent a substantial improvement in a disease setting where for many years no improvement has been observed. And the safety profile that we observed was acceptable with manageable and monitorable side effects.

In particular, the improvement was not coming with any increased significant toxicity here, and the PK/PD analysis supports the 50-milligram at the currently reduced dose. In the currently ongoing phase 3 study, we're evaluating

an approach where we use a loading dose of 20 milligrams for the first cycle followed by the 50-milligram for the subsequent cycle here with the intent that that might help you to get earlier to steady-state condition and further improve the benefit-risk balance of olaratumab.

This phase 3 study, a randomized, double-blind, placebo-controlled study, is currently underway. We plan to enroll 460 patients that have been already actually enrolled, and we expect the results early in 2020.

So besides this clinical observation in the adult population, the further development for the pediatric indication is informed by the non-clinical data that we have generated for the molecule.

The way we envision to come together is, on the one side, is the pre-clinical data that we have already in hand -- and I will talk to that in a second -- as well as the data that emerged from our phase 1 study in the pediatric indication, as well as further pre-clinical data on the other side that

we are currently generating in collaboration also with the Innovative Medicine Initiative in Europe, which gives us further opportunity to study in the pre-clinical models for pediatric indications; and to bring that then all together as a package, to have discussion with thought leaders, cooperative groups, and regulators to design an efficacy study that we currently envision to be a randomized, double-blind, placebo-controlled study, potentially in osteosarcoma, rhabdomyosarcoma, or other tumor types based on emerging data.

The non-clinical data that we have seen so far stems from cell lines as well as from xenograft models, and in particular, cell lines, osteosarcoma and rhabdoid have been identified as the most significant in terms of activity.

We further study then rhabdomyosarcoma, osteosarcoma, synovial carcinoma, and rhabdoid tumors, and the xenograft model. And taken together, also here, osteosarcoma seemed to be a particularly interesting tumor type for the activity of olaratumab.

To illustrate that, here are two examples. You see here xenograft models treated either with controlled cisplatin, the olaratumab as monotherapy, or the combination. And what we observed is certainly there is single-agent activity with olaratumab, but it is in combination with the chemotherapy where you see the most activity.

What's interesting actually is when you then look not only at the total numbers for the group with the tumor growth inhibition, but rather look into the individual animals here as a waterfall plot, what we see there is that chemotherapy or olaratumab as a monotherapy just gives us the tumor growth inhibition, but it is only the combination where some of the animals show tumor regression.

That's actually an observation we have seen in other models for osteosarcoma as well. We her in this particular HU09 model looked for combination either with cisplatin or with doxorubicin. Again, olaratumab had single-agent activity here, with the most activity, again, in

combination with chemotherapy, and a very similar picture like before, when you look into the individual animals.

Cisplatin alone and doxorubicin alone may need tumor growth retardation, but when you combine with the olaratumab, you see some of these animals with a regression in tumor, indicating that you might shift here the biology from a pure tumor growth retardation actually to a phenotype where you see regression of the tumor.

Other tumors that we have studied pre-clinically included rhabdomyosarcoma and rhabdoid tumors. We haven't seen any activity in rhabdomyosarcoma in the two models that we have so far studied. There is some challenge in identifying good models for rhabdomyosarcoma. Whereas in the rhabdoid tumor, we have seen activity in a xenograft model with expression of PDGF receptor alpha, here, the single-agent activity led to tumor growth inhibition in almost all of the animals, as you can see at the bottom of the slide.

So the information from this non-clinical as well as the observation from the soft tissue sarcoma in the adult population, all of that influenced moving forward into the phase 1 study I would like to present next.

This study is a phase 1 dose-escalation study that is evaluating the monotherapy as well as the combination of olaratumab with three different chemotherapeutic regimens. Patients eligible for this study are pediatric patients less than 18 years old with a solid tumor that are refractory treatment or relapsing.

By the design, first cycle of the treatment is with the monotherapy of olaratumab to understand the single-agent tolerability in the pediatric population. And after that, patients then will be based on investigator's discretion to one of the three different chemotherapy regimens combination, which are either olaratumab plus doxorubicin, or olaratumab plus vincristine and irinotecan, or olaratumab in combination with ifosfamide.

The following year, a dose-escalation

approach, we started the dose with 15 milligrams, and only if that is tolerated as a single agent, the patient is allowed to move on with the 15 in the combination. If not, the plan is to deescalate here to 10 milligram per kilogram.

The second part of the study would be the next dose level, which is the 20 milligram per kilogram following the same scheme of monotherapy followed by the combination therapy. The primary objective of that study is to identify a dose that can be safely administered either as monotherapy or individually with each of the different chemo combinations here. So these arms are considered to be separate and not necessarily leaving into the same combination dose.

A few words about the dosing strategy that informed here the decision for this dose escalation. So the aim was to achieve a similar exposure with olaratumab as we have seen in adult patients in the phase 2 study in combination with doxorubicin. And by doing similar modeling here, either following the assumption that the

relationship between clearance and body weight might be preserved as observed in the adult patient population or elemetric dosing scheme, we have found that according to the simulation, either a 15- or 20-milligram per-kilogram dose, might be the one achieving this exposure that we have seen in the adult population to be linked with activity.

For that reason and also considering the safety here, we started at the 15-milligram and have the plan to move up to the 20-milligram dose level guided by the tolerability and the PK observation. And if data indicate, further dosing regimens might be explored to achieve the goal to get to the same exposure level.

So to conclude here, the non-clinical data that we have at the moment gives strong support particularly for osteosarcoma as a tumor type of interest. Our phase 1 study is designed to provide us the safety for the monotherapy as well as for the combination therapy, with combinations of standard-of-care therapeutic regimens commonly used in the pediatric population.

The phase 1 study is planned to enroll up to 70 patients. Currently, we have enrolled 18 patients, and we expect to complete the study by June 2019 at the latest. And the ultimate idea would be then, together with the pre-clinical data, to bring that together, maybe some signal observed out of the safety and tolerability study, to inform the design of the study I mentioned before, the randomized efficacy study later on.

To conclude overall, we see the PDGF receptor pathway to be one of relevance in several pediatric tumor types, including the rhabdomyosarcoma, osteosarcoma, and rhabdoid tumors. And the clinical benefit observed with doxorubicin in adult patient population for us has the potential also to influence the cause of disease in the pediatric population, and that is why we're committed to study those.

The phase 1 study is on the way and will allow us to establish for the first time in a pediatric patient population the safety and tolerability in combination with chemotherapy. And

upon availability, we want in discussion with cooperative groups, external thought leaders, and the agency to design the efficacy study in tumor types, including osteosarcoma, potentially rhabdomyosarcoma, or further tumor types of interest.

With that, I would like to thank you for your attention and move on to questions and the discussion.

DR. PAPPO: Thank you very much. Before we proceed, I would like to ask Anne to introduce herself for the record.

DR. ANGIOLILLO: Good morning. Anne Angiolillo from Children's National Medical Center. Thank you.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you. We will now take clarifying questions for Eli Lilly. Please remember to state your name for the record before you speak. And if you can, please direct questions to a specific presenter. And I'll take a shot at the first question.

On your adults soft tissue sarcoma trial, did you see any signal of any particular subtypes that were more sensitive to the combination or not? And the reason for that is, could that be translated to other histologies in pediatrics that are common in pediatrics, but not -- on some of the histologies, I have just seen adults are not applicable to pediatrics; for example, synovial sarcoma or malignant peripheral nerve sheath tumors.

DR. MELEMED: I'll have Dr. Wacheck come in and discuss the efficacy by subtype that we saw in a pivotal trial.

DR. WACHECK: So we did an analysis to better understand here, particularly histologic subtypes. And the limitation that we had in that originally designed phase 2 study, with only about 63 patients in each of these arms, is that we ended up with, in part, very, very small subsets of tumor.

We stratified according to histology with leiomyosarcoma and others, but the subset of the

others sometimes goes down to 2 to 3 patients, so that we didn't feel that we can do any meaningful conclusion out of that.

DR. ARNDT: Thank you for that clear presentation. One question. Do you have any pre-clinical data on the combination of olaratumab --

DR. MELEMED: It's hard for us to say, too.

(Laughter.)

DR. ARNDT: -- and irinotecan or the investigational agent plus ifosfamide?

DR. MELEMED: I'll have Dr. Stancato come up and discuss the pre-clinical data.

DR. ARNDT: And the second question, I'll have a follow-up question after that.

DR. STANCATO: Hello. Dr. Lou Stancato, oncology translational research. Regarding your question about combination with irinotecan and -- I'm sorry; what was the other agent?

DR. MORROW: Ifosfamide.

DR. STANCATO: Ifosfamide. We have looked at combinations in synovial and rhabdomyosarcoma. Unfortunately, we did not see increased efficacy of

olaratumab or of the chemotherapy, so no combination effect. And that came with no obvious signs of increased toxicity. However, the combination was inactive in those two separate tumor types.

DR. ARNDT: So then the justification for using the agent plus doxorubicin is obvious, especially given your clinical trial, but can you talk a little bit more about the justification of combining it with the other two agents if there was no observation of enhanced activity in the pre-clinical model?

DR. STANCATO: For that, I think I'll ask Dr. Wacheck to come up.

DR. WACHECK: As Dr. Stancato mentioned, the pre-clinical data that we have currently are limited to just a few models. And based on the fact that the ability to combine with commonly used standard-of-care chemotherapies or regimens -- encouraged us to evaluate here the safety and tolerability, also knowing that the predictability of pre-clinical data, and

particularly when it comes to combination therapy, it's sometimes limited in terms of predictive value.

So before excluding here a regimen that is commonly used just on two animal models, we felt that this might not be sufficient, but further pre-clinical data were generated to support this hypothesis.

DR. ARNDT: The other question was, you mentioned that there were some challenges with the doxorubicin model. Are there plans to do further pre-clinical investigation in rhabdo?

DR. MELEMED: Dr. Stancato, can you come up to discuss the challenges in that model?

DR. STANCATO: Lou Stancato, oncology translational research. The challenges are that, by and large, patients express the PDGF receptor alpha to a very high degree and typically ligand as well. The majority of the models that are available to us do not express the PDGF receptor alpha, and therefore make it very difficult for us to analyze direct effects on the tumor.

So that's a challenge we're trying to overcome through external collaboration with experts in the field.

DR. WEIGEL: Brenda Weigel, University of Minnesota. I have four questions, and hopefully they'll be brief. The first one relates to the toxicity seen in the adult JGDG study. And I note that there's a difference in the median number of cycles received between the olara-dox and the single-agent dox. It's noted that 7 cycles for the combination were administered as a median in 4 for dox alone.

Do you have any data to suggest that the difference in some of the toxicities that you have seen are really because of the cumulative effects in additional cycles, and have you done a cycle-to-cycle comparison?

DR. MELEMED: Dr. Wacheck, can you come discuss the toxicities seen regarding the cycles?

DR. WACHECK: So I definitely would like also to remind my colleague from the statistical part to come on, on deck, Dr. Peterson.

Particularly, let me clarify whether I understand your question correctly. Are you referring to the doxorubicin-specific toxicity, particular cardiotoxicities, or in general?

DR. WEIGEL: No, in general because you noted that there was an increased number of overall AEs reported on the combination arm. Is that purely because the patients had almost double the number of cycles as a median and it's because we're getting cumulative additional, particularly cumulative toxicities in later cycles that is driving that toxicity that you're saying?

DR. WACHECK: I think that's a very good point. And we looked from an efficacy perspective in terms of the additional number of cycles for doxorubicin. But for the adverse events, I would ask whether Dr. Peterson could comment on that and the analysis.

DR. PETERSON: Patrick Peterson, clinical statistics. So we did look at the extent of cumulative toxicity. We didn't see any evidence of that. If you consider, for example, the increased

rate of neutropenia that was observed with the combination, most of that was observed in the first or second cycle. If patients were going to have neutropenia, it was observed early, so there's no cumulative effect.

DR. WEIGEL: Thank you. My next question relates to the trough targeting and the pharmacokinetics. And if I'm understanding correctly, the cycles are 21 days, and the data presented were achieving a trough of 66 at the end of cycle 1. However, olara reaches steady state at approximately day 50.

What data do you have that says if you look at steady state, particularly cycle 2, 3, and beyond, the number of patients that actually achieved that? And what is the data driving the loading dose? And do you have any modeling or human data, or any data to say that that actually achieves a higher percentage by day 21?

DR. MELEMED: Yes. I'll have Dr. Cronier discuss the exposure response analyses that were done to actually explain the loading dose.

DR. CRONIER: Damien Cronier, PK/PD pharmacometrics. So with respect to the first point in how the exposure response analysis was performed, we actually examined two PK endpoints. The primary concern was because we were dealing with phase 2 data, we had a relatively small number of patients to look at, to look into. So we selected our PK endpoints for us to preserve the integrity of the sample size.

So this is why we looked at the trough level at the end of the first cycle, because it does represent the first intent to treat. And it does make it possible to have the full sample size, because no patients will have left treatment because of disease progression, nor will those reductions have happened yet. So that's the rationale behind looking at the trough level at the end of the first cycle.

We also did look at the average concentration throughout the entire duration of treatment. So we modeled the PK profile throughout every cycle of treatment for each patient,

calculated the total AUC throughout the entire duration of treatment, and then divided this value by the duration of treatment.

That made it possible to do two things, keep all the patients within the analysis and also take into account the effect of dose reductions on the overall exposure throughout treatment so as to avoid biases linked to looking at one snapshot over time. So that's with respect to how the endpoints were picked and chosen.

We did not really see a difference in the shape or the nature of the exposure-response relationship with either endpoint selected. So in both cases, the half-maximum C mean 1 and C average, respectively, were superimposed with the 25th percentile of the endpoint within the trial.

So that's with respect to I think your first question. Now, with respect to the loading dose, when we examine the trough level at the end of cycle 1 during the exposure-response relationship analysis, what we observed is that patients in the lower quartile, so patients whose PK endpoint was

below the EC50 value, did not receive much of an overall survival benefit, but also seemed to progress within the first 2 to 3 cycles, seemed to experience earlier disease progression.

So this observation made us generate a pharmacological hypothesis that perhaps people did not receive an overall survival benefit because they did progress too early. And so we then thought that using a loading dose approach, by using 20 milligram per kilogram on day 1 and 8 of the first cycle, would make it possible to try and push the trough level to higher values and try to rescue some of this risk of early disease progression and try to keep patients on board for longer.

The additional layer to that decision was that we wanted to also manage the Cmax value in order to maintain the positive benefit-risk ratio, so we thought a loading dose approach will make it possible to achieve steady state as soon as administration, number one, and maintain the overall Cmax within the range of values explored

within the phase 2.

Now, with respect to what this is yielding in terms of outcome, we do not know yet because the phase 3 trial is still ongoing. So we're hopeful it's going to help patients some more, but we will only be able to just talk about this once we have gathered and examined all the data.

DR. WEIGEL: I appreciate that and thank you. That was a great answer.

My third question shifts gears -- actually, all my things shift gears -- you alluded there is I believe an ongoing study in adults with CNS primary tumor. Can you speak to CNS penetration in patients who have been treated with the drug who have had CNS primary tumors or CNS metastatic disease, and if there are any plans to explore patients with CNS tumors further, especially since this is a high area of need in the pediatric population, and what pre-clinical data might exist to support that?

DR. MELEMED: I'm going to have Dr. Melemed discuss the general plan on the CNS program per se.

DR. S. MELEMED: Dr. Symantha Melemed. I'm the product team leader for olaratumab. So the study that you're referring to is a glioblastoma trial that we did in a phase 2 setting. We did not see substantial activity for this drug in that setting. And then I'll turn to Dr. Stancato in terms of the pre-clinical.

Okay. We have limited pre-clinical data there as well, so for the most part, we aren't pursuing that as that setting.

DR. WEIGEL: Thank you.

My last -- and it's not really a question; it's more a comment. It's alluded to in the potential proposed plans for a pediatric study, the use of a placebo. And I think I would really caution against pursuing that in the pediatric space.

I think it's pretty much a non-starter in the pediatric space to offer a placebo versus standard of care. I think they are very, very difficult trials to enroll to and I would encourage thought around another comparator or some other

approach rather than randomized to a placebo.

I appreciate the randomization design, and I understand that. I think I would just really caution against the inclusion of a placebo.

DR. MELEMED: I would love to get FDA's feedback on the regulatory nature by not having the placebo and what that would entail from a regulatory perspective.

DR. REAMAN: I think the regulatory perspective for these rare pediatric tumors require some flexibility. And I think Dr. Weigel's absolutely correct. We would have difficulty supporting a placebo in a disease setting that's life-threatening and in a pediatric population.

So I think there are ways to consider randomization and to also try to isolate the effect of a particular product, particularly in a combination setting. But I think the use of a placebo would be difficult.

DR. MELEMED: To clarify, you'd be open with an open-label trial with a standard arm and an experimental arm, so it's a two-arm trial, but just

not double-blind, placebo-controlled? Is that what you're saying?

DR. REAMAN: Yes.

DR. MELEMED: Thank you.

DR. ANGIOLILLO: Hi. Anne Angiolillo from Children's National. Dr. Wacheck, you certainly shared your enthusiasm with me. Thank you. That was a great presentation. I have four different questions, varied; some are very simple, others a little bit more in depth.

With regards to the fever neutropenia with these patients, did they receive growth factor, Neulasta? Yes.

DR. WACHECK: Yes, they received.

DR. ANGIOLILLO: So yes.

DR. WACHECK: Yes.

DR. ANGIOLILLO: You mentioned the infusion-related reactions. Could you elaborate on that? Was the drug stopped? How was it handled? Were patients pre-medded? And that then bleeds into -- on a double-blind study, I couldn't figure out how that would work, et cetera.

DR. WACHECK: Yes.

DR. ANGIOLILLO: Thank you.

DR. WACHECK: So in the phase 2 study, there was not a strict regimen in terms of any pre-medication to be used here. And as mentioned, the infusion-related reaction, having seen in the first 1 or 2 cycles mainly, chills, some rigor, some rash were the most common events here.

Moving on into further studies, we now have a pre-medication scheme that patients in the first cycle receive corticosteroids as well as an antihistamine. And then for subsequent cycles, at a minimum an antihistamine, but based on investigator's discretion, obviously, for the pre-medication it can be used.

In case of a previous infusion-related reaction, there is the need to pre-medicate with corticosteroids as well as with antihistamines.

DR. ANGIOLILLO: As far as performance status and eligibility, can you speak more to that?

DR. WACHECK: So with ECOG, performance status of 1 or 2 were allowed in the study.

DR. ANGIOLILLO: With regards to the tumor regression in animal models, were anti-angiogenesis markers looked at, like the EGF or histologically?

DR. WACHECK: We didn't do any analysis with respect to anti-angiogenesis. There was analysis done or tumor collected to look at PDGF receptor alpha expression and to see whether there was any correlation. And it turned out that there wasn't in that limited sample size to a tumor, as well, any correlation being identified. I think here the analysis was limited by a mix of primary and fresh tumor biopsy, metastases as well as primary tumors and a sad and relatively small sample size.

DR. ANGIOLILLO: It might be interesting to look at those patients that had their frank regression and start with that. Thank you.

DR. ROTH: I have two questions. The first is kind of a pharmacovigilance question, so I don't know if there's a right person. But the adult trial of doxorubicin and this agent, the cardiac dysfunction is labeled as not significantly different. I don't know exactly when that

evaluation took place. For example, if it took place after a couple cycles, I wouldn't be surprised not seeing any difference. But as a practitioner, you'd kind of like to know that maybe, in the combination, I need to worry more about cumulative dose of doxorubicin at 300 as opposed to 450.

So I was wondering how long that cardiac evaluation represented there was or whether maybe six months after the completion of therapy you'd be worried about it, so that's my first question.

DR. MELEMED: I'm going to first do a clarification on the dose pre-meds. When patients were getting doxorubicin and they were in that trial, they were also getting dox pre-medication, so either getting some dox pre-medication, and then we continued it with the monotherapy, so just to put it in that perspective.

Regarding the question regarding cardiac toxicity, the trial was done mainly in the U.S., and patients were given Zinecard after certain cycles to help with the cardiac toxicity. But I'll

have Dr. Volker talk specifically about the timing of the exams that were done for the cardiac toxicity.

DR. VOLKER: So echocardiograms as well as mover [ph] scans were done throughout the study here, and in patients also further follow-up. The recommendation was to do this type of study. I don't have the exact number of how many scans were done or echocardiograms in the follow-up year.

DR. ROTH: Yes. I'd actually feel a little bit more comfortable if actually this agent changed the PKs of doxorubicin, but since there's more acute toxicity attributed to doxorubicin in the absence of PK alterations, that made me wonder why wouldn't you have an effect on potential cardiotoxicity down the road?

DR. WACHECK: I think it's an excellent question, and I don't have an answer right now for you. But it's definitely something to think about.

DR. ROTH: Thank you. My second question is on JDDN [ph]. I don't have a lot of concerns about getting DLTs in that initial run-in with the agent.

But the question is, if then you get your first dose of this agent plus doxorubicin, what's the de-escalation scheme? Are we deescalating the study drug? Are we deescalating a known -- maybe the most active agent? So I was just wondering what the de-escalation schema would look like.

DR. WACHECK: So as I said, not withholding a standard of care, the first would be a de-escalation here for the antibody and the dose. And according to the protocol, it would be 10 milligram per kilogram to be administered. If there are other toxicities that are potentially linked with it specific to chemotherapeutic regimen, the protocol foresees that there is also dose escalation for these respective chemotherapeutic agents.

DR. ROTH: Actually, I'll give you an example. So for example, grade 3 mucositis with the first course of the combination, there would be de-escalation of the doxorubicin?

DR. WACHECK: Within the protocol, according to different side effects, it's a guideline how

that would need to be handled. We're in very close contact also with our investigators to get their input here and to understand what the patient situation is exactly about.

DR. ROTH: Thank you.

DR. MacDONALD: Tobey MacDonald, Emory University. A couple more questions with regard to mechanism of the drug and appropriate selection of patients or interpretation of results. Rather than expression of the receptor, did you look at downstream signaling? And was there any correlation with responses in pre-clinical or clinical models?

DR. MELEMED: I'll have Dr. Stancato discuss what we have regarding the pathway for olaratumab.

DR. STANCATO: So regarding downstream signaling elements, in particular phospho-AKT, phospho-ERK, we have looked at the effect of drug treatment on tumors, and we see a cessation or basically a blockage of stimulating element like AKT or phosphorylation. However, to this point, we don't see any correlation.

Actually, let me think about how I want to address that. In almost all cases with olaratumab treatment, we see blockade of the signaling pathways. That doesn't necessarily always tie into an anti-tumor effect. But we don't get an anti-tumor effect in the absence of signaling blockade, if that makes sense.

DR. MacDONALD: Yes, it does. So my next question is, you didn't show -- are there other kIT family members of which this antibody binds to?

DR. STANCATO: Not that we're aware of.

DR. MacDONALD: Okay. And also the same -- so for the rhabdomyosarcoma xenograft with PDGF receptor expression, but did not seem to respond to the drug --

DR. STANCATO: Correct.

DR. MacDONALD: -- have you looked at either mechanism of resistance or an alternative mechanism for survival for that cell?

DR. STANCATO: We have not, and it's something that we plan on doing. Really, to do what you're asking, we need a more expansive set of

tumor models so we can then begin to compare and contrast. So the answer to your question is no, but it is in the plan once we can identify models that meet that criteria.

DR. MacDONALD: Just one suggestion. If you block receptor signaling in the PDGF receptor, there is cross-localization with the eGFR receptor, and you can actually activate eGFR through that mechanism. So again, I'm not sure if you've looked at alternative partners for signaling because that could be an explanation for some of your responses or lack thereof.

DR. STANCATO: Yes. You are correct, and in particular, even within the PDGF receptor family, the beta receptor can heterodimerize with alpha. And we're exploring what effect that has on olaratumab treatment and efficacy.

DR. MASCARENHAS: Leo Mascarenhas, Children's Hospital Los Angeles. I have a couple of questions related to the JDG trial and a question about toxicity. So that pivotal trial had a very modest effect on progression-free survival,

but an impressive effect on overall survival.

What do you postulate that difference to be due to?

DR. MELEMED: We did see effect both in PFS and overall survival, and it was more prominent in overall survival. I'm going to have Dr. Wacheck come and discuss that from an olaratumab perspective.

DR. WACHECK: Historically in soft tissue sarcoma, the correlation between PFS benefit and overall survival benefit is not a strong one. There have been studies showing PFS benefit, but no OS benefit. In our setting, there was an improvement in both, but it isn't in the range of the literature that this concordance between PFS, or in other words, the predictive value of PFS for OS also in our study underestimated the OS effect based on the progression-free survival.

There is thinking about biological rationale, and we are looking in the pre-clinical models to further understand given the fact that we not only have an effect on the tumor, but as well

on the microenvironment to understand whether that provides some rationale here to think that the overall survival benefit is seen.

For the further development, it begs for us the question what is an appropriate endpoint to study in an efficacy study moving on. And to that extent, we would greatly also appreciate the feedback of this committee, whether that should be OS or whether there are other endpoints potentially being considered, given a particular pediatric population that is a relatively far endpoint with overall survival.

DR. MASCARENHAS: Yes. So in pediatrics, most often, PFS correlates extremely well with overall survival, and so it's different. I mean, to that extent -- I think we have one example in osteosarcoma where it was slightly discordant, but otherwise, in general, almost every trial -- if I'm not mistaken, PFS has correlated extremely tightly with overall survival, so that's a relevant issue.

The next thing, just given the mechanism of olaratumab and the pathway, there could be some

concerns with wound healing. So what was your experience on the JGDG trial, and if there were any issues, how were they managed and handled with relationship, especially being treated to an antibody?

DR. WACHECK: To the best of my knowledge, I don't recall any particular case in that study where that was a major point of discussion. And by that, we lack here experience to share how that was handled.

I think you're also thinking about the biology in normal tissue and the fact that we were in a metastatic setting, so the patient didn't have any immediate surgery here, made it maybe less likely to observe.

DR. MASCARENHAS: Yes. So just an osteosarcoma, potentially, I mean, surgery has a pretty big role both in newly diagnosed as well as metastatic disease and recurrent disease. So that may be of some relevance and that's the reason I asked that question.

The last question was related to

hematopoietic toxicity. So when olaratumab was combined with doxorubicin, there was a little more hematological toxicity. And my question is, have you noticed a difference in your studies thus far with the higher dose of 20 milligrams per kilogram versus 15 milligrams per kilogram in combination with chemotherapy as related to complications with myelosuppression?

DR. WACHECK: So we have seen with other chemo combinations that it can -- agrees [indiscernible] known myelosuppression for these specific compounds, but not that the 20 milligram per kilogram had a significant effect in terms of the higher incidence of any myelosuppression in this study, certainly still on small sample size. And we have studies currently running to look in a larger population with a 20 milligram per kilogram. So I think at the moment it's a preliminary answer I can give.

DR. MASCARENHAS: Thank you.

DR. GORLICK: Richard Gorlick, MD Anderson Cancer Center. Sorry, once again, a series of

questions. My first one is very much in the weeds. So HU09, I know, is a cell line, not as a PDX model. Do you have it as a PDX model, or is this a cell line growing in PDXs?

Similarly, I'm not familiar with the CTG1095 line. Do you know the source of that line or anything about its characterization?

DR. MELEMED: I would love to answer those, but I think I'm going to call on Lou Stancato for that.

DR. STANCATO: Regarding the HU09, you're correct. It's a cell line that then is grown as a more or less traditional xenograft model. The CTG is actually one of the few commercially available patient drive xenograft models. And in this case, it was from Champions. I'm not sure on the treatment status of that model coming in, but it's definitely an osteosarcoma PDX model.

DR. GORLICK: Cool. PDGFR seems to be a biomarker of response to this class of drugs. Have you thought about making PDGFR expression a requirement for treatment? Do we know whether the

expression is driven by amplification or other things that make it irreversible?

Then the final part of that is, how have you looked to explore where PDGF is expressed in pediatric tumors to try to identify potentially sensitive histologies?

DR. MELEMED: In the phase 2 pivotal trial, we did specifically look at PDGF expression, and I'll have Dr. Wacheck discuss that specifically and then discuss what other options we're looking at.

DR. WACHECK: As mentioned, we looked in the phase 2 study with two different immune histochemistry assays. The first one that was also used for the stratification in that study showed an 89 percent expression in the tumor samples assessed. We learned later, retrospectively, that the specificity of that assay wasn't that high a source detecting the better form of the PDGF receptor.

Using another assay for the assessment, we have seen in about 36 percent of the patient positive expression, which links with some TCGA

data, showing that for an MRNA level, a similar range of positivity has been observed. We also moved on in looking into MRNA expression in these particular patients and whether the PDGF receptor MRNA correlates here.

But in line with the data we observed for the histochemistry, MRNA didn't help here to further identify patients that might particularly benefit from treatment. So at the moment, we don't have any plan to develop a biomarker around the PDGF receptor alpha.

DR. GORLICK: The final part of it was, how did you look through pediatric tumors, with TCGA, or did you use anything to try to look at what pediatric tumors may express PDGF?

DR. WACHECK: For that, I would like to invite Dr. Stancato to speak to the data generated.

DR. STANCATO: So with regard to your question about expression of the receptor, a combination of TCGA analysis as well as immunohistochemistry across a variety of pediatric histotypes.

DR. GORLICK: Next question is, I know we've talked about this topic in many ways, but I sort of wanted to touch on it more directly. I am inferring that you have not given olaratumab plus doxorubicin in the context of a prior doxorubicin-treated patient. Are you worried about that? Are you going to, when you approach that, limit the prior anthracycline exposure?

What data do you have about giving olaratumab to patients at each amount of doxorubicin exposure?

DR. MELEMED: I'll just say in general -- but I'll have Dr. Wacheck discuss in a little more detail. But the intent right now for the trial is to do dox naïve. Again, I think the challenge could be enrolling that population. But that's the plan right now.

Dr. Wacheck, want to talk any more about what the plans would be or what else we could be doing there?

DR. WACHECK: Yes. As I mentioned, the cumulative toxicity is one that limits here the

opportunity to look in that question in particular. We don't have a dedicated study to exactly addressing the question you are asking here, and for that reason, I don't have really any data I can offer for you.

DR. GORLICK: Extrapolating on that answer or further, to just clarify, so the JGDN study precludes prior anthracycline exposure? Is that true?

DR. MELEMED: Yes. The question back to the panel would be, would you change design, what would you do? I mean, I think the concern would be, most kids are getting a cumulative dose of dox, which is going to be significant. How would you model that, and would you add that?

We thought so far not to, but there is going to be I think a challenge of enrollment in that population. But there is that risk-benefit question here, and I'd love your advice on that.

DR. GORLICK: Are you limiting histologies in that JGDN study or it's all-comers?

DR. MELEMED: It's all-comers. It's a

standard phase 1.

DR. GORLICK: Any reason to believe that olaratumab is going to be effective as a single agent, or do you think it needs to be combined for likely efficacy?

DR. MELEMED: I'll have Dr. Wacheck discuss that, but in general, it's thought as being in combination.

DR. WACHECK: I have a two-part answer for you. Most activity I think is really in combination with the chemotherapy, but there's anecdotal evidence, not only pre-clinical but also in clinical, for instance, in the glioblastoma study discussed before, where patient had a partial response to the treatment.

We don't have any biomarker at the moment that would help us here to predict it, but I cannot exclude that there are patients with single-agent activity.

DR. GORLICK: Thank you.

Questions to the Subcommittee and Discussion

DR. PAPPO: Thank you very much. And we do

not have any more time for questions. Sorry. We have to move to the next part of the agenda. There will not be an open public hearing session during this part of the meeting.

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 observers, public attendees may not participate except at the specific request of the panel. We should start with the first question.

DR. DOROS: Based on the nonclinical and clinical data presented, please comment on the relevant cancers that should be studied and potential endpoints that could be used in future clinical trials designed to evaluate the efficacy of olaratumab in pediatric patients?

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

DR. GORLICK: Richard Gorlick still. So I

think critical is actually evaluating a little bit more detail, the spectrum of pediatric tumors that's sort of express PDGF and sort of enhancing the pre-clinical data. Clearly, initiatives like the PPTC could be used to profile. Again, I don't know offhand whether they express PDGF receptor or not, but that should be easy to ascertain and could give you some histologies.

The challenge for developing any therapy like this is in the context of sarcomas is just about every sarcoma patient who has a chemosensitivity disease will see anthracyclines with rare exceptions. The rare exceptions probably don't lead to enough patient availability to ask a meaningful question. I think for pediatrics, it's going to be critical to tackle the topic of this drug combined with dox or single agent at minimum after doxorubicin.

I think the challenge is going to be single agent. If we're not convinced it's efficacious, you're going to have to figure out what you can combine with post-anthracycline to give a

meaningful chance of seeing activity. Thank you.

DR. PAPPO: Leo?

DR. MASCARENHAS: So I agree with Richard, and I think I would encourage a generation of more pre-clinical data if possible, particularly with rhabdomyosarcoma. I think to seek collaborations because there are several rhabdomyosarcoma xenograft models, so at least you can expand the pool with that area. The PPTC, as Richard said, is another option. And in terms of expression, potentially with tissue microarrays and various patterns of -- I mean, tissue arrays of various patterns of pediatric tumors might be an option.

The interesting thing is given the mechanism of action and history with certain other tumors, rhabdoid tumors are particularly interesting. I think there was a St. Jude clinical trial.

Was it called ANGIO-1 [ph] study, where there was a patient who was treated with their anti-angiogenic therapy with a rhabdoid tumor who had prolonged partial response? And your pre-clinical data, that's an area of great need

potentially in pediatrics, a very poor prognosis tumor where you may not necessarily need to do a randomized trial or anything. The historical controls are very, very stable in that particular disease. So potentially a single-arm combination trial might be worthwhile.

The other area or two areas potentially where there is a potential role is in hepatic tumors. And these are rarer populations in pediatrics, but there is data to suggest that there may be some activity of these compounds.

The other thing is in a subset of renal tumors. For example, you have poor outcomes in patients with anaplastic Wilms tumor as well as in certain relapsed Wilms tumor who have been pre-exposed to anthracyclines and radiation therapy.

So there may be some opportunities to do some pre-clinical work with this agent to explore further development.

DR. PAPPO: Thank you. There was also other tumors such as desmoplastic Moran's small round-cell tumors that the chimeric transcript increases

PDGFR expression. It's a very rare tumor with a high need because those patients are usually incurable.

Can I address the sponsor for a question also?

Is PDGFR expression necessary on all of these tumors? Because I am -- or are you modulating other things like the microenvironment, et cetera, that perhaps that's what you're doing, and it's not necessarily related to the primary tumor. And that dates back to do we need to screen lots of other tumors and only those that have PDGFR expression are the ones that you're going to target or not?

DR. STANCATO: So you rightfully point out that receptor expression exists both on the tumor and the supporting environment; in particular, with cancer-associated fibroblasts, which is an area that we're becoming increasingly interested and excited in for further research.

What I can tell you about the pediatric tumors, the non-clinical models that we work on,

receptor expression is necessary, but not sufficient. So we have models that express receptor that we've shown you today that do respond to olaratumab treatment, and we have models that express the receptor that do not. Why that is, we're still trying to understand.

DR. PAPPO: But if they don't express it, [inaudible - off mic].

DR. STANCATO: If there's no expression thus far, we have not found pediatric tumors that respond.

DR. REAMAN: What about the adult sarcomas? Can you comment on those?

DR. STANCATO: Non-clinically? So non-clinically, the adult sarcomas represent a bit more of a challenge as far as identifying models that respond. By and large, we see the greatest response rate, if you will, in pediatric tumors. Just a very limited subset of PDGF receptor alpha expressing adult models respond. But again, the same holds true. Receptor expression is necessary, but not sufficient.

DR. MELEMED: I'm going to add from the clinical perspective that in the PGF alpha antibodies that we looked at, we did not see a correlation. Now, it may not be the right tumor. It might not be the right stromal, how we did it. We're still further evaluating on how to do this, but it wasn't a standard response.

DR. MASCARENHAS: I just feel previously to share some thoughts about clinical trial design for evaluating this drug. I completely agree with Dr. Weigel that a double-blind placebo-controlled trial is not going to be feasible in pediatrics, and it's not attractive. People just want to enroll on that particular design.

If considering a trial in rhabdomyosarcoma, we now have robust progression-free data in first-relapse rhabdomyosarcoma, and I believe that should be the endpoint, either EFS or progression-free survival in that disease because we have almost 15 years of studies, which have really in pediatrics delineated that endpoint well.

Osteosarcoma is a little more challenging.

I think Dr. Gorlick can comment a little more, but there are some benchmarks that Children's Oncology Group has come up with in the a relapse setting potentially. Consideration for randomization in the metastatic population may be feasible depending on the strength of pre-clinical data potentially generated. I did comment on rhabdoid tumor already.

The last thing is a randomized phase 2 pick-the-winner design is also an efficient way to consider moving it ahead. It may not be sufficient for registration, but would definitely give us an idea about further developing this agent within pediatrics.

MS. LUDWINSKI: Donna Ludwinski, Solving Kids' Cancer. I also was curious with regard to the single-agent use, if there's any rationale to look at it in an MRD setting such as after primarily metastases are removed and osteo. It may not be applicable, but it's a question.

DR. PAPPO: Any other comments or questions? Richard?

DR. GORLICK: Just responding to what Leo said, what's being alluded to is in the context of osteosarcoma, you have a very robust historical control. So it's relatively easy to do single-arm phase 2 trials against the historical control because it is so stable. The biggest factor that defines prognosis in this group of patients is resectability.

So you can do it in an MRD state or in a bulk disease state. They're relatively straightforward small patient trials. Again, the challenge that was mentioned prior is all of these patients will have had 450 milligrams per meters squared of doxorubicin at the time of relapse and that's universal.

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

(No response.)

DR. PAPPO: So I want to try to summarize this. So the first thing is that we recommend that you expand your spectrum of testing using the PPTC and other xenografts and also try to identify PDGFR

expression in pediatric tumors that could potentially benefit from this agent.

In the setting of a relapse trial, it will be probably relatively hard to accumulate patients with sarcomas since the vast majority of these patients have had anthracyclines with pretty large doses, 375 to 450 milligrams per meter squared.

Other potential histologies that should be given consideration to the use of this agent include rhabdoid tumor. That's a great medical need, also liver tumors, subsets of renal tumors, and desmoplastic small round-cell tumor.

In addition, we also discussed the fact that PDGFR expression is necessary but not sufficient for the agent to have activity. Therefore, we truly support your strategy to continue to test virus, pediatric tumors for PDGFR expression to potentially select subsets of histologies that could benefit from this agent.

As far as protocol design, one of the possibilities would be a randomized phase 2 pick-the-winner trial. Another potential use would be

single-agent olaratumab in patients who have had all of their pulmonary metastatic disease in osteosarcoma resected.

I think that's pretty much it. Did I miss anything? Yes?

DR. MELEMED: Can I ask a question? This is a question for the FDA because we've heard about pick-the-winner trials before. What is the FDA's perspective on using a pick-the-winner trial to meet requirements from that aspect? So it helps us to understand from an FDA perspective.

DR. REAMAN: I guess I would just ask what do you mean by requirements. I mean, we're here really to discuss the design of studies that could be incorporated in a written request. We recognize that not all of the studies in a written request are ultimately going to be designed to potentially lead to approval for a specific indication given the challenges in doing pediatric studies, the length of time that might be required, and the fact that there may actually be no exclusivity incentive available to the sponsor for trials that look at

definitive efficacy.

DR. MELEMED: So I'll clarify. So a written request, you'd say that --

DR. REAMAN: So to answer your specific question, a randomized phase 2 study, a pick-the-winner study as part of a development plan that would be incorporated in a written request would be quite appropriate.

DR. MELEMED: Then the next step for -- if you wanted actually labeling for an indication --

DR. REAMAN: And then the next step would be a study that would be designed with input from the agency pending the results of the pick-the-winner study.

DR. MELEMED: Thank you.

DR. REAMAN: Can I just add one more? I think the other tumors that might be appropriate to evaluate here would be the non-rhabdo soft tissue sarcomas. Although they're relatively uncommon in the pediatric age group and very heterogeneous, it was those tumors in adults that you saw activity. So I think that's certainly one group that could be

considered.

Just another note -- and I am fully supportive of an enrichment strategy or at least a plan to evaluate whether there is a requirement for PDGF receptor expression. But I would encourage you to think about any assay that you develop yourselves or co-develop with another sponsor to seek input from the Center for Devices early on as you develop that, as either a complementary diagnostic or a companion diagnostic.

DR. PAPPO: Thank you. We will now proceed to question number 2.

DR. DOROS: Please comment on the safety profile of single-agent olaratumab and possible toxicities that may be seen when olaratumab is added to multi-agent combination therapy in pediatric patients.

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

DR. WEIGEL: So to summarize a lot of comments made around the table, I think one of the

challenges is that olaratumab appears to be targeted for development in combination predominantly with doxorubicin. And doxorubicin is pretty much part of most upfront regimens for the vast majority of pediatric solid tumors. And the adult data thus far that is presented is in doxorubicin- or anthracycline-naïve adults.

So a couple thoughts on potential strategies and other approaches, we certainly have developed drugs and done early-phase trials in pediatrics in combination with doxorubicin. The two things I would encourage some thought around are a potential strategy is taking the combination into very high-risk pediatric populations that are newly diagnosed.

So I think that is a possibility to consider. Those are small populations, but those are potentially doable with some of the histologies that have already been mentioned, desmoplastic small round-cell and other rhabdoid tumors, some of the highest risk hepatic tumors, et cetera.

I think that's one potential strategy. I

think another strategy is to obtain data in adults who have had anthracycline exposure. And then typically, when we have had that data, we have been able to very quickly design an early-phase or phase 2 trial in children where we have very clear historical cutoffs of anthracycline exposures, monitoring and have mandated the use of cardioprotective strategies, and have not required a lot of additional data. But we have had the data at least in a small subset of adults, recognizing that the cardiac risk factors in adults are very different than children. However, I think there are a couple strategies to address that.

But I do think, given the tremendous, I think, push to move this into upfront therapy with anthracyclines requires some thought behind the next steps.

DR. MASCARENHAS: So I think there is some useful data which will be generated from the JGDN trial with the arms, which potentially could address treatment cassettes, which are used in upfront therapy, particularly with ifosfamide and

its relevance to osteosarcoma.

I think the doxorubicin cohort is going to be challenging, but potentially could understand that we do have precedent in pediatrics for taking the doxorubicin dose up to 600 milligrams per meter squared and higher in osteosarcoma patients. So a potential strategy could be to allow doxorubicin exposure, provided your exposure is up to 450 milligrams, and mandate cardiac protection for all those patients.

For example Ewing sarcoma patients are given typically 375 milligrams per meter squared. They would likely receive a first-salvage therapy, which everybody considers the standard. But after that, it's any therapy, and they become candidates for a phase 1 trial.

Similarly, osteosarcoma patients, a frequent question, which is asked by parents is those drugs worked well the first time; why don't you use them again? Now, we know the reasons why we don't use them again, but there is also old data from the '70s where doxorubicin was used as palliation for

patients with sarcoma who previously had received doxorubicin and did have some temporal benefit for that.

So there is precedent to actually potentially considering modifying the trial, if you have issues related to accrual on the doxorubicin arm, to actually get data, which would make you consider using an upfront.

I fully agree with Dr. Weigel's suggestion about very high-risk patients like rhabdoid tumors or widely metastatic rhabdomyosarcoma potentially, high-risk disease, infusion-positive rhabdomyosarcoma, may be something to consider.

DR. RAETZ: Elizabeth Raetz. So one of the things that I noticed -- and it seems like the monotherapy was well tolerated, but there was over 50 percent of patients who had greater than grade 3 neutropenia. And importantly, it didn't look like that led to a high number of infectious complications. But in a pediatric population, that might be important to follow.

I might have missed it, but just with the

design of the part A and part B of the dose escalation, I didn't know if within this, you're going to separately look at olaratumab with different combination cassettes, but you might have very different toxicity profiles. So I think to optimize the dose of the antibody, it might be important to look at that distinctively with each of the populations.

DR. ANGIOLILLO: Anne Angiolillo. Thank you. As you're considering different tumor types, I think it'd be interesting to look at the microenvironment in the bone marrow because we know, in the world of leukemia at least, that's all revved up with regards to angiogenesis, so just something to consider.

DR. GORLICK: The COG has conducted and published a study of trastuzumab plus upfront chemotherapy for patients with newly diagnosed metastatic osteosarcoma. It's a model for how you can conduct that type of trial, that has a cardiotoxicity risk.

DR. PAPPO: Any additional questions or

comments regarding question number 2?

(No response.)

DR. PAPPO: So I'm going to try to summarize this. It is clear that perhaps the path forward is a combination trial, olaratumab with a variety of agents. Specifically as it relates to doxorubicin, one potential strategy to use this combo is to apply to newly diagnosed high-risk patients, for example patients with metastatic sarcomas or patients with widely disseminated rhabdoid tumors or other histologies.

Also, it will be important to get additional information from the adults regarding the anthracycline exposure and what were the outcomes of these patients.

There is a precedence in pediatrics to giving higher doses of doxorubicin, up to 600 milligrams per meter squared. So one potential strategy could be to allow previous treatment with doxorubicin up to a certain dose, whether it's 375 or 450, and then add cardioprotection and do an arm of olaratumab with doxorubicin.

It is important to consider that the toxicity profile of different cassettes in combination with olaratumab might be very different, so that's something to keep an eye on.

There is also a precedence for incorporating an agent in patients with metastatic osteosarcoma with very, very strong monitoring of cardiotoxicity, which was the trastuzumab trial. So that may potentially serve as a model for something in newly diagnosed metastatic patients with osteosarcoma.

Do I have any other things that I missed or that summarized it?

(No response.)

DR. PAPPO: Okay. We will go to question number 3 now.

DR. DOROS: Please comment on the feasibility of or requirement for international cooperative group collaboration in a future efficacy study.

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

will now open the question to discussion. Richard?

DR. GORLICK: So in the context of osteosarcoma, we conducted the EURAMOS study, which was an international European and North American consortium to answer a multitude of questions in osteosarcoma patients.

The need for an international collaboration was driven by the use of a biological stratification. If you're sort of assessing a single agent, you probably can do that in the context of a single cooperative group like the Children's Oncology Group without requiring international collaboration.

International collaboration is challenging. The EURAMOS study took multiple years to develop because of regulatory requirements by multiple groups in Europe along with North America. That said, it's feasible. It can be done if the question demands that sample size.

So the EURAMOS study had an over 2,000-patient accrual, and it has been completed and the results published, so it is feasible.

DR. MASCARENHAS: I echo Dr. Gorlick's comments. I think, again, larger studies are going to require a cooperative group or a major consortium to actually conduct, and particularly with rare subtypes of tumors. I think the Children's Oncology Group has successfully demonstrated the ability to conduct randomized phase 2 trials in rhabdomyosarcoma, and those could be completed if an appropriate comparator is found to be studied.

For rhabdoid tumors, a single-arm cooperative group study could be feasibly accomplished, but if a randomized trial is desired, it has to be an international collaboration, even if it is a randomized phase 2 for the number of patients, which you might need to address that issue.

DR. PAPPO: I would also like to add that another potential strategy would be to lower your age of eligibility if you're going to combine olaratumab with something else in a specific histology where some pediatric patients can be

treated.

For example, if you do a specific study with synovial sarcoma, why restrict it to 18 and older? You can put patients of 12 years of age or older, and that could encompass the vast majority of that subgroup of patients, and you would increase your sample size without needing to do an international study.

There's also more data and evidence to suggest that, for example, COG now has collaborative initiatives with liver tumors, for example, so it's a more common thing that we're seeing now. And I agree with Leo that for very small populations, it may be very necessary to do an international trial if you're going to target, for example, only rhabdoid tumors. Or if you want to target very rare PDGFR-expressing solid tumors, for example, I believe that you would need an international strategy there.

Greg?

DR. REAMAN: I would just also support the concept of international collaboration because I

suspect that there's a plan to work with the European regulatory agency. And I think it actually facilitates clinical trial design, and conduct, and completion if there is some agreement to collaborate, cooperate, and coordinate development plans and not have competing studies.

So although the EURAMOS study was difficult, it was difficult because it was the first NCI-supported cooperative group study that was done internationally, and there were no guidelines, and we basically created the guidelines as we developed the EURAMOS collaboration.

I think things would be much easier now, quite honestly, too. And then there have been multiple international collaborative studies done in diseases, particularly in rare diseases, in Ph-positive ALL and in the chronic myelogenous leukemia.

So I wouldn't discount or I wouldn't be overly concerned about the regulatory hurdles of international collaboration as you think about these studies because I think the issue of finding

doxorubicin-naïve patients is really going to create a rare population of patients. It's going to mandate international collaboration.

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

(No response.)

DR. PAPPO: So to summarize very briefly, we are supportive of international collaborative studies, and the challenges that were faced earlier might have been mitigated now that we have a little bit more experience on how to conduct these studies.

We will now proceed to question number 4.

DR. DOROS: Please comment on the sponsor's plan to evaluate platelet-derived growth factor receptor expression in pediatric cancers during their proposed development program.

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

DR. MASCARENHAS: I'm sorry. Can we clarify the sponsor's plan on this? Because I didn't sort

of hear a clear plan.

DR. WACHECK: For the pediatric study, it is an exploratory objective to look at that, and we have an optional biomarker sampling here. I think the question might be asked in the broader context. Given that we have a mandatory tissue collection in the adult study ongoing with the phase 3, what is your perspective in terms of implementing in a future pediatric study the use of biomarker around PDGF receptor alpha?

DR. MASCARENHAS: I think requesting archived tissue of its newly diagnosed patients' diagnostic tissue to assess this is not going to be a problem. The pharmacodynamic studies do look at signaling post-exposure, if there's no planned surgery in pediatrics, that could potentially be a problem. However, if it's going to be used up front in the diagnosis of high-risk patients, often surgery is still a part of the plan, and there is an opportunity to evaluate that.

I don't think we are still at a point where we could mandate biopsies for the sake of research

purposes without a therapeutic decision being made on it, though that's an evolving field and might become feasible.

DR. REAMAN: I think one thing to take into consideration is if continuing pre-clinical evaluation does demonstrate a stronger correlation between expression and activity of this product in pediatric tumors, I think there could be an increasing role for mandated biopsy prior to going on studies, if there's really an opportunity that something is going to predict outcome.

So I wouldn't preclude that as a possibility, but again, it would really depend on how strong the data is for a correlation.

DR. ROTH: Building on that, just a word of caution from the adult world in the example of metastatic urothelial carcinoma, where we have 5 PD-1s approved for the last 12 weeks, some with a companion diagnostic, some without a companion diagnostic.

The word of caution is, I appreciate the data that you've not yet seen any evidence that

PDGFR expression was necessary for a response. It may not be true for the next tumor type. So for example, in urothelial carcinoma, the response rate in PD-1 high expressers over 1 percent was with the first drug approved as 26 percent. It was 9 percent in PD-1-negative tumors. Well, it turns out that 9 percent is comparable to this current standard of care for second-line therapy, so why do the companion diagnostic?

So I just didn't want you to get -- this kind of becomes a self-fulfilling prophecy. You get boxed into a corner where all of a sudden, that becomes a requisite for eligibility because you might be missing something off target.

DR. GORLICK: Some will discuss the ethics of mandating archival tissue. And the ethics of mandating archival tissue are sometimes driven by the availability of the drug outside of the context of a clinical trial.

So for a drug that is available for other indications, the patient is now being denied the opportunity to get the drug because they could get

it outside the context of the clinical trial. So as long as it's a licensed agent, there should be no reason that you can't mandate the receipt of archival tissue.

The upfront biopsy and re-biopsy, I think in pediatrics, it still continues to be a standard that if it's a purely research question, the ethics of that is probably not the same as adults. If you're talking about whether it produces clinical benefit, then it becomes identical to the adult situation.

If you believe this has a negative predictive value, meaning absence of PDGF, the patient shouldn't be treated with this drug, there would be no problem mandating biopsy, particularly in a patient population where there's a risk of toxicity.

So if you would not give the antibody to somebody who doesn't express PDGF, then mandating that biopsy becomes very easy, but that becomes an eligibility criteria then for your trial, and you'd have to have sort of an assay that you can run in a

CLIA certified manner.

DR. MacDONALD: I think because you have such a robust signal of activity in the adult study, it's almost imperative to do your exploratory investigation.

I don't know what sequencing or other studies you're planning, but I think those results should be available, which would facilitate the idea of getting a biopsy mandated and also direct your attention rather than being a second exploratory, of which you don't know what you're looking for. But since you have the signal, you should be able to find some distinction between those two groups if you do a global-based approach.

DR. PAPPO: Can I ask the sponsor how are you evaluating PDGFR positivity in the adult trials, and how do you find that it's positive or negative? Is it by IHC or do you do PCR, or what do you do?

DR. S. MELEMED: So for the phase 3 study, we have the second IHC that we have validated to be specific to PGFR alpha, so we're doing that

retrospectively after the patients have been enrolled. In addition, we have the PCR-based assay that we're looking at as well.

DR. PAPPO: So both of those can be done on archival tissue, right, on paraffin-embedded tissue?

DR. S. MELEMED: That is correct.

DR. PAPPO: So that answers that. Thank you.

Any additional questions or comments regarding this question?

(No response.)

DR. PAPPO: So I think that the sponsor needs to think a little bit more about if they're going to require PDGFR expression in one way or another for eligibility of patients in this particular study. The issue of re-biopsy might be problematic unless there is an obvious clinical benefit or an obvious need for that to be a marker to administer the drug.

Let me see if I'm missing anything else. Anybody else want to add anything? Yes?

DR. REAMAN: I just want to clarify the issue of re-biopsy. So re-biopsy to me means you enroll a patient on the study, you have a biopsy, but then at some point during the study, you re-biopsy to either look for effect, some PD effect, or molecular affect.

What I was suggesting before was if there is strong data to support that the only patients who respond to this agent are those whose tumors express PDGFR, then there would be a potential prospect for direct clinical benefit for a patient to undergo a biopsy prior to going on therapy because you would be making a treatment decision based on the results of the biopsy. And alternatively, if their tumor was negative, there would be no reason for them to be exposed to a potentially toxic drug and enrolled on the study.

So I think biopsy and re-biopsy, re-biopsy in a relapsed protocol setting could be used as an eligibility requirement for that relapsed study.

DR. PAPPO: The fact that you can do this, though, on archived tissue brings the issue of

re-biopsy --

DR. REAMAN: I mean, obviously, if they can do it on archived tissue, that's fine.

DR. PAPPO: Right. Tobey?

DR. MacDONALD: But I would say that since we're not talking about an amplification or oncogenic driver, it's a very real possibility that your PDGFR expression could change over time and treatment. And that re-biopsy before treatment is probably a better indicator than the actual diagnostic biopsy.

DR. PAPPO: Thank you. Leo?

DR. MASCARENHAS: Sorry. Just a clarification. I'm a little confused with re-biopsy. My interpretation was, once you're enrolled in a trial, if you want a second biopsy to look at the effect of the drug, that was the biopsy which I was talking about, which may not be feasible in pediatrics at this time. But a diagnostic biopsy at the time of relapse prior to enrollment usually may be justifiable. Yes.

DR. PAPPO: Right. If you do not have

tissue available, that's a requirement for eligibility, yes.

DR. MASCARENHAS: Right. Yes, as a requirement for eligibility.

DR. PAPPO: I was talking about that type of re-biopsy, not a re-biopsy --

(Crosstalk.)

DR. REAMAN: It's definitely justifiable.

DR. MASCARENHAS: Yes. It is justifiable.

DR. WEIGEL: Yes. I would echo that. I think it's definitely justifiable, and particularly if it's tied to the real potential for benefit.

DR. PAPPO: The secondary biopsy to assess a pharmacodynamic effect, that's a completely different issue.

DR. MASCARENHAS: Yes, right.

DR. PAPPO: Thank you. We will now proceed to question number 5.

DR. DOROS: Given the recent approval of this product in adults with soft tissue sarcoma, please discuss whether evaluation of olaratumab in pediatric non-rhabdomyosarcoma soft tissue sarcoma

should be considered.

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

DR. WEIGEL: Brenda Weigel. I would say the short answer is yes, and the reason for that is the spectrum of non-rhabdo soft tissue sarcomas are different in children than they are in adults, predominantly. And a subanalysis was not presented from the adult trial, but historically, the adult trials have been mainly populated with liposarcomas and leiomyosarcomas that really do not occur in children.

Where we would be most interested in these tumor types have been certainly raised is tumor types such as synovial sarcoma, which tends to be the most common non-rhabdo soft tissue sarcoma in children. And there are a couple strategies that could address this, which would be a separate arm in a trial or expansion of adult trials to lower ages of those histologic subtypes.

I think there are a few approaches that

could be taken, but I do think we can't assume and lump all the non-rhabdo soft tissues together.

DR. MASCARENHAS: I echo Dr. Weigel's comments, but with some qualifications or a slightly different opinion. I don't think we would learn anything from a pediatric-specific non-rhabdomyosarcoma soft tissue sarcoma study.

However, participation in certain cohorts with separate analysis on an adult clinical trial, since a large number of these patients are teenagers and we don't expect the PK or the toxicity of this agent to be different -- and the examples would be synovial sarcoma, malignant peripheral nerve sheath tumor, and undifferentiated sarcoma -- the other subtypes are vanishingly rare, and there's limited information to be gleaned from pediatrics.

DR. PAPPO: Maybe you will have additional information with the ongoing trial about specific histologic subtypes that could potentially be expanded into a larger study for a specific histology. And that would be probably what would

be very advantageous for younger patients, 12 or older, to be enrolled in that trial.

Any additional comments or questions?

(No response.)

DR. PAPPO: So to summarize this question, the answer is yes, but in very specific cohorts and to consider the possibility of, if you're going to have a specific adult clinical trial for a specific histology in which there's a higher prevalence of that histologic subtype in pediatrics, to consider lowering the age to 12 or higher so they can be enrolled in that trial.

Anything else?

DR. MASCARENHAS: I would just ensure that the pediatric perspective is incorporated in the design of that clinical trial going forward, rather than just design it as an adult trial and then ask children to participate in it.

Adjournment

DR. PAPPO: Thank you very much. We will now take a 15-minute break. Panel members, please remember that there should be no discussion of the

meeting topic during the break, amongst ourselves, or with any member of the audience. We'll resume at 10:25 a.m., so it's a little bit longer than 15 minutes.

(Whereupon, at 10:03 a.m., the session was adjourned.)