FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUTAION AND RESEARCH

PEDIATRIC SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

Topic 2

Wednesday, June 21, 2017

10:10 a.m. to 11:47 a.m.

FDA White Oak Campus

The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Lauren Tesh, PharmD, BCPS

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Alberto S. Pappo, MD

(Chairperson, pedsODAC)

Member and Head, Division of Solid Malignancies

St Jude Children's Research Hospital

Professor of Pediatrics

University of Tennessee Health Science Center

Memphis, Tennessee

Courtney J. Preusse, MA

(Consumer Representative)

Senior Research Administrator and CLIA Operations Director

Fred Hutchinson Cancer Research Center

Seattle, Washington

Bruce J. Roth, MD

Department of Internal Medicine

Division of Medical Oncology

St. Louis, Missouri

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS

(Non-Voting)

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

(Industry Representative)

Executive Medical Director, Amgen Oncology

Therapeutic Area Head, US Medical Organization

One Amgen Center Drive

Thousand Oaks, California

TEMPORARY MEMBERS (Voting)

Carola A. S. Arndt, MD

Professor of Pediatrics and Consultant

Division of Pediatric Hematology/Oncology

Department of Pediatric and Adolescent Medicine

Mayo Clinic College of Medicine and Science

Rochester, Minnesota

Steven G. DuBois, MD

(Participation in Day 1)

Director, Experimental Therapeutics

Dana-Farber/Boston Children's Hospital

Associate Professor of Pediatrics

Harvard Medical School

Boston, Massachusetts

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

Aviva Krauss, MD

(Participation in Day 1, Topic 2)

Medical Officer

Division of Hematology Products (DHP)

OHOP, OND, CDER, FDA

C O N T E N T S

P R O C E E D I N G S

(10:10 a.m.)

DR. PAPPO: We're going to get started. We will now proceed with topic two, PM01183, lurbinectedin from Pharma Mar USA, Incorporated. Dr. Lauren Tesh will read the conflict of interest statement for this session.

Conflict of Interest Statement

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

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations. The following information on the status of this committee's compliance with the federal ethics and conflict of interest laws, covered by but not limited to those

found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

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

their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

This session's agenda involves information to gauge investigator interest in exploring potential pediatric development plans for three products in various stages of development for adult cancer indications. The subcommittee will consider and discuss issues concerning diseases to be studied, patient populations to be included, and the possible study designs in the development of these products for pediatric use.

The discussion will also provide information to the agency pertinent to the formulation of written requests for pediatric studies if appropriate.

The product under consideration for this session is PM01183, lurbinectedin, presentation by Pharma Mar USA, Inc. This is a particular matters

meeting during which specific matters related to Pharma Mar USA, Incorporated's product will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. However, for the record, we would like to disclose that Dr. Lia Gore has been recused from participating in this session.

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

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

We would like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which the FDA participant has a particular personal or imputed financial interest, these 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 might have with the firm at issue. Thank you.

DR. PAPPO: Thank you, Dr. Tesh. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any

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

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

Industry Presentation - Arturo Soto

DR. SOTO: Thank you very much and good morning, everyone. My name is Arturo Soto, and I am the director of clinical development at Pharma Mar. Today, I would like to present some data regarding lurbinectedin that will serve for the discussion of the development time in the pediatric indication.

Today, I will start talking about the

mechanism of action, then some sort of review about the regulatory history of this compound. Then I will present the preclinical data that supported the clinical studies. And also, importantly, I will show some data regarding our experience with this drug in adults and also from this trial the information that is relevant for the pediatric indication.

After that, I will present what we have thought about pediatric development, and finally I will express some potential challenges for the clinical development of this drug in the pediatric indications.

Starting with the mechanism of action, first of all, I would like to say that this drug, lurbinectedin, is a second generation of another drug that is currently approved in the U.S. for the treatment of soft-tissue sarcoma, trabectedin. Both drugs are related, but we have detected that lurbinectedin has important differences in terms of pharmacology, safety, and also efficacy.

The main message for today regarding

mechanism of action -- because of what we have investigated a lot on the mechanism of action of lurbinectedin, we can tell many more things. But the most relevant for today's session is that lurbinectedin is a transcription inhibitor.

What does this mean? Lurbinectedin first is bound to the DNA, to the CD-rich sequences, which are mainly located around the promoters of protein-coating genes. Then this binding produces the starting of the elongating, so the RNA polymerase II has to be elongated to be [indiscernible] and degraded by the ubiquitin/proteasome machinery.

Then there is the recruitment of specific endonuclease, such as XPF and ERCC1. And in attempt to revert the break that has been -- or the alteration that has been produced by this complex, there would be the production of DNA breaks that will deal finally with apoptosis.

You know very well that cancer cells aberrantly deregulate specific gene expression programs with critical function in cell

differentiation, proliferation, and death. And it's today well known that this altered gene deemed programs in cancer cells have striking dependence on continuous active transcription, what has been called transcription addiction.

Perhaps one of the main examples of these tumors with transcription addiction is Ewing sarcoma. Ewing sarcomas are rare tumors and account for about 2 percent of all childhood cancers. And it's very well known that specific translocation between chromosome 11 and chromosome 22 results in the generation of the Ewing's FLI1 chimeric gene that produced the chimeric protein.

This protein functions as an active transcription factor that is the hallmark of Ewing's sarcoma. This translocation is present in over 85 percent of the patients with this disease.

Ewing's FLI1 alters the expression of approximately 1,000 genes, and many of these are involved in malignant transformation, metastatic potential. It then also facilitates angiogenesis,

the evasion of senescence, and directly or indirectly produces inhibition of apoptosis. This has been not so only in Ewing sarcoma, but also this has been the most triggered. This transcription addiction is present also in many other tumor types.

In these relatively recent papers, this relevance is stressed, and I would like to mention because for today's discussion it will be relevant that this transcription addiction has been shown in triple-negative breast cancer, small-cell lung cancer, soft-tissue sarcomas, and ovarian cancers.

Going back to the potential effect of lurbinectedin in patients with Ewing sarcoma, apart from the effect on the degradation of RNA polymerase 2, lurbinectedin also produces a target block in the binding of Ewing's FLI1 to its target genes. Also, it has been demonstrated that redistribution of Ewing's FLI1 in the nucleus is produced with lurbinectedin. The result has been in vivo a complete reversal of Ewing's FLI1 activity and the elimination of established tumors.

This has been everything that I wanted to recommend regarding the mechanism of action, and now I summarize the related history of lurbinectedin. The initial investigation of the new drug application for lurbinectedin went into effect in January 2009.

Since then, 19 clinical trials have been completed or are today ongoing, and these have been conducted in Europe, mainly in Europe and the U.S. In July 2012, lurbinectedin received the orphan drug designation for the treatment of ovarian cancer in the U.S. and in the European Union.

In October of 2016, the FDA agreed on a full waiver for the initial pediatric study for the treatment of patients with extensive-stage small-cell lung cancer. The orphan designation was an indication of ovarian cancer. And today, lurbinectedin is not approved in any country.

Now I'm going to focus on some non-clinical data. This slide presents those regarding the pharmacokinetic characteristics. This drug after administration to mice, rats, dogs, and cynomolgus

monkeys have demonstrated to have a long terminal elimination half-life, slow plasma clearance, and large volumes of distribution. The Cmax and AUC are proportional to the dose, up to the MTD, byre both after single or repeated doses.

The regulator, lurbinectedin, has been distributed in rats, and the maximum concentration is observed in the spleen, liver, lymph nodes, thyroid glands, lung, kidney, and small intestine. The lowest radioactivity was detected in brain and testes.

The feces have been shown to be the main route of excretion in the rat, more than 90 percent in the first week post-dose. Oxidative metabolism is very intensive and mainly is driven by CYP3A4. And lastly, lurbinectedin is highly plasma protein bound.

I have brought here this graph, although it's not from non-clinical data. It shows very well the differences with trabectedin I mentioned before. Here, you can see in green-yellow the AUC for lurbinectedin given as the recommended dose

that was obtained in the first phase 1 trial, compared to the AUC of trabectedin. That is the small piece that is in the left bottom part of this graph. So the exposure to lurbinectedin is more than 15 times higher than that for [indiscernible].

On the contrary, what we should have expected, the half-life is 3 times lower, so this higher exposure probably is driven by differences in distribution processes.

Regarding non-clinical data again, but now focused on safety and toxicology, there were no concerns related to neurotoxicity, cardiovascular, or respiratory functions. The people doing non-clinical studies were performing up to 4 cycles in rats and cynomolgus monkeys, and the one with 8 cycles is currently ongoing.

The clinical signs that I have to highlight in these studies are transient body weight decreases, diarrhea, and emesis. The mortality in these animals was related to bone marrow suppression, hepatic alterations, and gastrointestinal events. It was common also in the

decrease in blood count cells, especially neutrophils. And in animals, it was seen that the hepatotoxicity was mainly an increase in liver function tests, hepatocellular necrosis, and biliary damage.

Again, I wanted to put here some data in humans where you can see that we join the list, the trabectedin, the elevation of transaminases in the phase 1 that used the same schedule, 1-hour infusion that we are using with 1183, many patients had grade 3 or even grade 4 transaminase elevations. But with 1183, only in 7 percent of the patients treated in the first phase 1 had these elevations of transaminases, and no patients had grade 4 transaminase elevations.

So this is just to show you the differences in terms of pharmacokinetic properties in the prior slide, and here the differences in the safety profile.

Regarding clinical trials in adult patients with cancer, today we have treated more than 1,000 patients with lurbinectedin in Pharma Mar's

sponsored clinical trials. The recommended dose of single agent is 3.2 milligrams per meter squared, and in combination, the dose ranges from 1.2 to 2.2 milligrams per square meter.

The most relevant adverse event associated with lurbinectedin are hematological, mainly dose-dependent neutropenia. Other adverse events were mild to moderate gastrointestinal events and fatigue. And efficacy was observed in different tumor types with single agent or in studies in combination.

This is a brief summary of all the trials we have conducted up to now with lurbinectedin. Starting with a single-agent phase 1 trial, the first one was using the 1-hour every-few-weeks infusion. So we started another one, trying to split the dose into the days 1 and day 8 maintaining the periodicity of 3 weeks. And then we started another phase 1 in acute leukemia patients. Phase 1 in combination, we have done. Some are completed and some are ongoing with doxorubicin, gemcitabine, capecitabine, paclitaxel,

paclitaxel plus bevacizumab, cisplatin, and even irinotecan.

Regarding phase 2, no randomized trials, we have conducted one in pancreatic cancer, one in breast cancer, and one basket trial, including up to 9 different indications of solid tumors. In phase 2, randomized trials were conducted in platinum-resistant or refractory ovarian cancer, using as control arm, topotecan, and another one in non-small-cell lung cancer of lurbinectedin, one arm, second arm, lurbinectedin plus gemcitabine, and the control arm, docetaxel.

Today, we are conducting two big phase 3 trials, one in platinum-resistant ovarian cancer, using PLD or topotecan as control arm and another one in small-cell lung cancer with, on this occasion, not lurbinectedin alone, but combined with doxorubicin, and the control arm is the sufficient choice between CAV or topotecan.

Now I'm going to show you a summary of the efficacy that we have found in these different indications using first lurbinectedin combined with

other drugs, and after that used as single agent.

In this slide, you can see on the left part, the activity we have observing endometrial cancer in combination with doxorubicin. The total patients included were 32, and 37 percent of them had responses including 2 patients with partial response with complete [indiscernible] responses. In combination with paclitaxel, where we include 10 patients, the response rate was 30 percent.

Regarding ovarian cancer, we included these patients in many of the combinations that we conducted in phase 1. The numbers are relatively small. For example, the highest bar is impressive, but we have to say that there were only 3 patients in which all of them responded, and 1 out of 3 had completed responses. But also, we observed responses in combination with gem, 40 percent; with paclitaxel, 33 percent; and with cisplatin, 20 percent.

In small-cell lung cancer and metastatic breast cancer, also from phase 1 studies in combination, on the left is a combination with

doxorubicin treating second-line small-cell lung cancer patients, where we had a 50 percent response rate. We take into account the 5 patients that were treated in the same trial. In the third line, the same disease, small-cell lung cancer, the response rate was 20 percent.

In combination with paclitaxel, only 7 patients were included, but a response rate of 71 percent, including 1 patient with a complete response.

In breast cancer, again, the number of patients included in each study is quite variable, but in general, we have observed a level of activity -- for example, for doxorubicin, it was more than 60 percent; gemcitabine, 17 percent; capecitabine is the number of patients more relevant with 28 patients and a response rate of 54 percent. And with paclitaxel, among 12 patients, 58 of them had partial responses.

Regarding the clinical trials, phase 2 trials, using single agents, so not in combination, lurbinectedin, the first one that I want to comment

is a clinical trial in BRCA-1 or -2 mutated metastatic breast cancer patients. In this trial, we included 54 patients, and the response rate was 41 percent.

In the basket trial I had mentioned before, out of the 9 indications that were included initially, we had responses in 6 of them. Particularly in metastatic breast cancer patients with a mutation at the BRCA gene, we are in the 33 percent range of response rate.

In the small-cell lung cancer, we included up to now a total of 23 patients, and the response rate was 26 percent. In endometrial, using 11 and 3 alone, it's 14 percent. In Ewing's family of tumors, we have included really more than 17 patients, but these are those that are evaluated for efficacy, and among them, 18 percent had responses. Less effect was seen in biliary tract tumors and neuroendocrine tumors.

This is the phase 2 randomized trial that we presented the results in ASCO 2014. This was, as I said before, a randomized trial. The control arm

was topotecan. The response rate was in the whole population 21 percent, but if we focus on the resistant, the platinum-resistant ovarian cancer population, the response rate went up to 30 percent.

In the right part of the slide, you can see how even with a relatively reduced amount of patients, the total number was 82. But even with this number of patients, we had significant differences in PFS and even in overall survival.

A couple of slides about the safety of the compound, because for the next discussion, I think that is very relevant. This is a slide that shows the adverse events ordered by frequency, and you can see how there are no events of grade 4. Some of them were grade 3, and the most frequent were nausea, vomiting, and fatigue.

But I would like to remark that this drug, at least in grade 3 and grade 4, does nothing about cardiac events, neurological events. The stomatitis is very low, and also this drug does not produce alopecia.

These are the labs, the safety regarding the labs' values after the administration of lurbinectedin. Here, it's clear that the drug induces neutropenia, up to 30 percent of the patients with grade 4 neutropenia and close to 20 percent of the patients with grade 3. Febrile neutropenia can be controlled and be lower than 10 percent of the patients.

As I said before, lurbinectedin produces elevations of transaminases in a reduced amount of patients, particularly practically zero percent grade 4 under about 10 percent grade 3 if we talk about more specific for liver damage that is ALT.

Now I'm going to present some data from these trials in adults that are relevant to the pediatric indications. The characteristics of the patients with Ewing sarcoma were included in the basket trial. The median age was 30 years. Most of the patients had ECOG-performing status of 0 or 1. The median body surface area was close to 2, and the prior chemotherapy lines were 1 in 5 patients, 2 in 12 patients, or more than 2 in 5

patients.

This is the response, not only those that had responses that were 3, so with a response rate of 18 percent, but also you can consider how there are many prolonged stabilizations. In fact, the disease control rate was 65 percent.

Here, I brought an image from a patient treated in France with lesions in lung, pleural, and mediastinum. And here you can see that after 2 cycles of lurbinectedin, one lesion in the lung was reduced and one impressive lesion in the mediastinum in the bottom part of this slide, that after 2 cycles of lurbinectedin, practically disappeared.

We think that we have three reasons to develop lurbinectedin in Ewing sarcoma. That is the mechanism of action rationale, the data that we have in adults and also the data we have in preclinical models. But really, the second indication that we'd like to develop in the pediatric patients is neuroblastoma.

Really, we don't have patients treated in

our clinical trials with this disease. The reason is that up to 25 percent of the patients with neuroblastoma have amplifications of the MYCN gene that is part of the family of the MYC gene. And this is associated with very high-risk disease and with very poor prognosis. MYCN protein is a DNA binding transcription factor known to cause malignant transformation in both in vitro and in vivo tumor models.

So this is everything regarding neuroblastoma, but we think that it's worth trying to see what we are observing until then. The plan that we have is presented in this slide. We will start with a phase 1 classic 3-plus-3 dose escalation. We will start with single agent in all-comers or we will not restrict here the population of patients. This would be a criteria of the physician if there is any possibility that one patient can benefit from this type of treatment.

The objectives will be to find the recommended dose, the pharmacokinetics in this

population, and of course safety. Then in parallel, we will conduct phase 2 expansion cohorts, in Ewing's sarcoma, in neuroblastoma with a MYCN amplification, and of course other tumor types where the phase 1 part of the trial have shown interesting activity.

In this case, the primary endpoint will be -- or the objective will be the confirmation of the recommended dose or also to find efficacy signals. And in parallel,, we will conduct combination studies with lurbinectedin, first to find the right dose with classical phase 1 escalation trials using combination. And then we will move the same case as in lurbinectedin alone to the phase 2 expansion cohorts in the indications, in the main indication Ewing sarcoma and neuroblastoma, and other, depending on what we have observed in the first phase 1 part of the trials.

Of course, if we find interesting activity, then we will have to discuss which type of phase 2 or phase 3 trials would be randomized or not,

depending on the frequency of the disease in this population.

In the beginning, we plan to include only patients that are older than 2 years, and one safety information for these groups is available. We will continue including patients of other subgroups, for example infants and toddlers from 28 days to 23 months of age, and term newborn infants from birth to 27 days.

This is my last slide. This is the enumeration of potential challenges for the clinical development of lurbinectedin in pediatric indications. The first is from the broader point of view. Lurbinectedin is given via IV, and the solution for infusion contains sucrose, sodium lactate, sodium chloride, or glucose as excipients. And sometimes this can be a problem for administering to children.

Oral presentations for pediatric are precluded because the drug has very low permeability, and in the studies that we have performed of bioavailability, this is below

5 percent. Also today, lurbinectedin needs to be infused in a volume of at least 100 milliliters, and the lower doses for these pediatric patients will require the optimization of lurbinectedin strength per vial and the infusion volumes to ensure accurate dose measurements to reduce the risk of dosing errors and to prevent subcutaneous lesions in case of extravasation.

Also, we're concerned because these drugs mainly metabolize in the liver, is the question of the liver maturation, that there's not a lot of clarity regarding when a liver or when a child can have or can be considered to have completely matured the liver in terms of cytochromes. Also, another issue to take into account for development of lurbinectedin in children is the low penetration in the central nervous system on the testes.

That's everything. Thank you very much for your attention.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you very much. We will now take clarifying questions for Pharma Mar.

Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter, and I'm going to start again with two very quick questions.

The administration, is it going to be over 3 hours or over 24 hours? Because that's how trabectedin is started, every 3, and then you went with 24. What is the schedule of administration of this drug?

DR. SOTO: We have tried only 1-hour infusion, and it has worked. So we didn't find any reason to increase or to go to more complicated ways of administering. So we were maintaining children the same 1-hour infusion schedule that we have done for all our trials in adults.

DR. PAPPO: Just out of curiosity, were there any patients with myxoid liposarcoma treated with this drug? Were you able to replicate the same results we saw with trabectedin or no patients?

DR. SOTO: No. In adults, there is one clinical trial, but we are not the sponsor. The

sponsor is an investigator in Harvard University. And he has made a trial with three arms in soft-tissue sarcomas. The problem is that they haven't included patients with liposarcoma, so we really don't know the activity there.

The results will be presented soon. But for the moment, we have no control over this as we are not the sponsor. We don't have an answer for this question.

DR. PAPPO: Thank you very much. Steve?

DR. DuBOIS: Steve DuBois from Dana-Farber, Boston Children's. A question about the ongoing Ewing's trial or the larger trial that includes a cohort for patients with Ewing sarcoma; what is the lower age range for that?

I ask because, as you know, Ewing's is largely an adolescent and young adult malignancy, so you could capture a significant proportion of patients with relapsed Ewing's just by bringing the age range of that trial down.

DR. SOTO: It was very complicated to include patients lower than 18. In fact, finally

the population is adults, so over 18. The median age that I presented in the slides is 30, but no patient below 18.

DR. DuBOIS: And that trial is ongoing or it's concluded?

DR. SOTO: It's ongoing.

DR. DuBOIS: It's ongoing. And in that trial, how did you define Ewing family of tumors? That's a somewhat controversial area these days. Did you require demonstration of an EWS translocation or what was the --

DR. SOTO: No. This was a big basket trial, and we really wanted to signs of activity of many tumor types, so we were not very exclusive trying to include criteria that could restrict inclusion of patients. It was left to the criteria of the investigator.

DR. DuBOIS: Then related to the neuroblastoma potential cohort, do you have data from adults perhaps with MYC-driven malignancies, not MYCN-driven malignancies, to suggest that patients with those tumors are more likely to

benefit from the agent?

DR. SOTO: For the moment, I have to say that we are performing pharmacogenomic analysis in all the patients that we are including in our clinical trials. These, as you know, sometimes is not so easy to get the tumor specimens, but we are doing a big effort trying to have these samples. But for the moment, the data we have analyzed, there are no patients with the MYC amplification.

DR. DuBOIS: Thank you.

MS. PREUSSE: Courtney Preusse, Fred Hutchinson Cancer Research Center. I have very serious concerns about the drugs that are used in combination with the proposed new drug and I am concerned about an underestimation of adverse effects.

I am very familiar with the breast cancer and ovarian cancer patient population and drugs treated for early-stage and metastatic breast and ovarian cancer. And I am aware that gemcitabine, capecitabine, paclitaxel, cisplatin, irinotecan are extremely toxic drugs associated with many adverse

side effects that can potentially lead to life-threatening side effects.

So I don't feel like that is well represented in this presentation. And I worry that slide 18 or 19 - sorry -- 18, I don't know if those are adverse effects in combination with those other drugs. But this gives me great pause when talking about using this in a pediatric population.

DR. SOTO: This table includes only patients from single-agent clinical trials. Of course, when we combined lurbinectedin with other drugs, the toxicity varied. But at the end, you have to define in this phase 1 clinical trial the right dose for both components or the three components of the combination.

So we have rich doses that are acceptable from our point of view. For example, we have very extensive experience using a lurbinectedin plus doxorubicin. And yes, of course the level of hematologic adverse events is high, including febrile neutropenias. But during the development of the big phase 1 trial, we included about

150 patients for a phase 1 trial, this combination with doxorubicin, and we tried to modulate how to manage these toxicities.

For example, in the beginning, for the first occurrence of grade 4 neutropenia, we mandate the use of DCSF, so not as a primary, but after the occurrence of the first episode of grade 4 neutropenia. If this grade 4 neutropenia persisted, then we will decrease one level the dose.

But this was not enough, and at the end, we had to make some adaptations of the dose. For example, initially, the dose of doxorubicin was 50 milligrams per square meter and at the end, the recommended dose was 40.

Using these adaptations, we moved also from a flat dose of lurbinectedin to a BSA-based dose, and this also decreases the number of patients with febrile neutropenia and neutropenia in general. And now we are quite confident that with a new dose of these 2 milligrams per square meter, lurbinectedin; 40 milligrams per square meter,

doxorubicin, we can accept the toxicity, especially the hematological toxicity.

With respect to any other concerns, for example, the combination with gem in terms of liver damage, there was nothing to be worried about. And other typical toxicities with irinotecan, for example, diarrhea, et cetera, with the same model, the same strategy of dose modulation, we could control quite well the toxicities.

MS. PREUSSE: A quick follow-up -- I guess I would have liked to see more of the data on how those adverse effects were treated, mediated, and also how long that you followed these patients, because some of these adverse side effects have late effects.

DR. SOTO: Yes. We have a relevant amount of patients that were on treatment for more than two years, so it appears that all these toxicities -- if the patient is responding and can continue receiving the treatment, the toxicities are not cumulative.

The measures that we have implemented,

especially because it's the main concern, the hematological toxicity, are working. In fact, for example, now in the phase 3 trial, we are conducting in small-cell lung cancer. Of course, I can't say anything because we are blinded to the data, but do know that we received individual reports of serious adverse events.

It appears there has not been serious concern, even in a big population in many, many sites, 160 sites, in more than 20 countries all over the world, where sometimes the conditions are not as controlled as in the phase 2 or in the phase 1 setting.

I can say that with all the measures that we have included in the trials, safe use, those adjustments, this has been very well controlled.

DR. ROTH: Bruce Roth, Wash U, St. Louis. Could you go to the next slide, please?

This is not insignificant hepatotoxicity. So my question is, in the combo trials that have combined this drug with primarily hepatically metabolized second drug, do you have any additional

safety signals? Do you have PK data on clearance of the second drug, more neuropathy with paclitaxel, or some other evidence that your second drug is being metabolized differently in the presence of this drug?

DR. SOTO: Yes. In all our phase 1 combination and sometimes even in phase 2 for a combination, we obtain PK samples. There is a slight interaction of lurbinectedin with doxorubicin in that there is a slight reduction in clearance, and it appears that this is consistent.

But this is our reflection of, for example, the decision of going back, and instead of 50 milligrams per square meter of doxorubicin, change to 40 milligrams per square meter. Perhaps, apart from the toxicity, these degrees in the doxorubicin clearance produced by lurbinectedin can have an impact.

We haven't observed for the moment any other relevant interaction with taxel, with paclitaxel, with irinotecan, and with all the rest of the drugs that were mentioned in the combination trials.

DR. ARNDT: Carola Arndt, Mayo Clinic. You might have already said that, but in your current ongoing Ewing study, what's the time interval for treatment? I ask because I'm trying to gauge the duration of the responses for those patients. Are the cycles 21 days?

DR. SOTO: Yes. In almost all the trials I have presented, the schedule is a 1-hour infusion every 3 weeks.

DR. ARNDT: Every 3 weeks. Thank you.

DR. WEIGEL: Thank you. Brenda Weigel, University of Minnesota. I have a couple of questions. Following up on the combination as well as single agent, are you noticing in your adult trials that you have to dose-reduce either the lurbinectedin or the other chemotherapeutic agent? And then once dose-reduced, are they able to continue with therapy or are they coming off? Do you have a sense of -- are you having to titrate the doses?

DR. SOTO: Yes, it depends. In Europe, we put different criteria for reducing one, the other

drug, or both, or if the combination involves three. For example, in the case of doxorubicin, we can go up to -- determine cumulative dose. And then we stop giving doxorubicin and then continue with full dose of single-agent 1183.

So there were all the cases you have mentioned. Sometimes we have to reduce. For example, if we find liver damage with gem, we start reducing gem. And then if it is persistent, we can consider reducing lurbinectedin, but we will put different criteria for each drug in the combination.

DR. WEIGEL: And as a single agent, the lurbinectedin, you're able to generally continue it at the recommended phase 2 dose, or are those patients in later cycles dose-reduced as a single agent?

DR. SOTO: Yes. In general, there is a proportion, a big proportion. I can't say the exact number, but I would say about 60 percent of the patients can continue with a starting dose, especially because of the modulation that we have

mentioned before.

The dosing history of this drug is quite complicated. We started with a recommended dose of 4 milligrams per square meter. Then in the first phase 1 trial, we didn't find any correlation between body surface area on clearance of the drug. We changed to flood dose, and we moved back when we had a pool, a more relevant number of patients from the phase 2, that in fact there was a relationship between some toxicities and body surface area.

So then we came back again to dose per square meter, and to try to decrease the level of neutropenia, especially for neutropenia, we reduced from 4 milligrams per square meter to 3.2. That is the dose that we are using today in the single-arm trials.

Using this 3.2, really, there are patients that still need it because their PK variability is quite high. There are still patients that need this dose reduction, but in general, the majority of the patients can continue with 3.2 alone, all the treatment.

DR. WEIGEL: Thank you.

My last question, I'll move on from combinations. You've alluded a couple times in the presentation to concerns about CNS penetration of the agent. Many of the tumor types that you've already studied would potentially have CNS metastatic patients in their population.

Do you have a sense, over the 1,000 or so patients that you've treated, of any concerns with escape of progressive disease specifically within the CNS or issues related to concerns about treating patients with CNS disease?

DR. SOTO: Yes. In fact, small-cell lung cancer patients are very common that they have to leave the treatment not only with lurbinectedin, but with many drugs because of the appearance of brain lesions. But of course, it's not too much, but we have one case where we have observed a reduction in the lesions in the brain.

So there is a lot of controversy on metastases in the brain on the primary tumors, whether the blood-brain barrier is maintained or

not. In principle, we think that the penetration is not going to be high, but we have one case, one clear case of activity in a tumor and the brain metastases of small-cell lung cancer.

DR. PAPPO: Before we proceed, I wanted to ask Dr. Angiolillo to please introduce herself for the record.

DR. ANGIOLILLO: Good morning. My name is Ann Angiolillo from Children's National Medical Center, Washington, D.C. Thank you.

DR. MASCARENHAS: Thank you for sharing that data on Ewing sarcoma in your basket trial. I am aware of preclinical data with this agent in Ewing sarcoma, but not in any other pediatric-type cancer.

Are you aware if there are any attempts to explore this further with pediatric xenograft models or potentially through the PPTB program to look for a signal in other pediatric cancers? That's my first question, and I have a second question after that.

DR. SOTO: Yes. The only data that we have

for the moment in specific pediatric indication is the data I have presented in Ewing sarcoma. But of course, as we continue with the development in children, we will proceed with the evaluation in the non-clinical setting. But we have not decided exactly the structure that we will follow to achieve that.

DR. MASCARENHAS: I think that's going to be fairly important. The response rate presented in Ewing sarcoma is modest, though the clinical benefit rate as a single agent is a little more impressive. But the management of those patients in pediatrics is managed with combination therapy, so exploring that preclinically will be of importance.

DR. SOTO: Yes. In fact, in Ewing sarcoma, we have made an extensive evaluation of the combination with irinotecan. And there is a strong rationale to think that this combination, irinotecan and lurbinectedin, will be very active in Ewing sarcoma. And we are very well advanced in the design and starting of our combination trial,

specifically with irinotecan in Ewing sarcoma patients.

DR. MASCARENHAS: Any reason to explore the combination with doxorubicin or gemcitabine?

DR. SOTO: For the moment, we want to observe hints of activity using single agent. And as I showed in my graph regarding our clinical development plan for pediatric patients, in parallel, we will consider a combination. With doxo, we know that there is a lot of synergism in there with all the topoisomerase inhibitors. So doxo would be a good candidate.

Gemcitabine, although we have seen good activity in some tumor types but was not so exciting, let's say, as with doxorubicin, with the rest of drugs provided, we will start doing some preclinical studies before embarking on studies with children.

DR. GORLICK: Richard Gorlick, MD Anderson Cancer Center. I have several questions, actually. So extending the question about the similarities and differences between this drug and trabectedin,

do you have any preclinical or clinical data to suggest the spectrum of activity rather than the pharmacologic properties are similar or different?

DR. SOTO: Are quite similar. In fact, all the studies that we have performed in terms of mechanism of action, in terms of PK in animals, in terms of MTDs achieved in the non-clinical studies, was very similar. Perhaps some difference is in the IC50s that we found for both compounds, but not very meaningful.

The main difference came in the clinical arena, where we observed huge differences in the PK profile. And we think that this is driving the differences in toxicity and the differences in the efficacy profile.

Today, we don't have any reason to think that there is something more relevant in these differences than the completely different behavior in terms of pharmacology.

DR. GORLICK: In a drug which is intended to inhibit transcription factor activity, do you think it is the AUC or the peak dose that's more likely

to define efficacy?

DR. SOTO: We expect the Cmax may peak. Why? Because with trabectedin, we conducted a phase 2 clinical trial in Ewing sarcoma patients, and there was no activity at all. But in this case, we gave trabectedin in 24 hours, and we have had impressive completed response in a phase 1 trial when the drug was given in 3 hours.

So one explanation for that finding is precisely that the activity was absent because of the lower peak that we achieved with a 24-hour infusion. Lurbinectedin is administered as a 1-hour infusion. And also, as you have seen, the PK is completely different, and we will obtain much higher peaks and much higher AUC. But we think that the peak will be important, especially for some addicted to transcription tumors as Ewing sarcoma.

DR. GORLICK: In the context of other malignancies, have you done any comparative studies of schedule at all to begin to decipher whether that's the case?

DR. SOTO: We have thought many times. Why? Because we have good activity, and we have asked ourselves what would happen if we gave this drug in 24 hours. But we have never decided to move into this complexity as we are having quite good results using the wire infusion. But we will still consider prolonging the duration of the infusion.

DR. GORLICK: Do you have any pharmacodynamic measures of efficacy, so anything that you can assess from blood or otherwise as a marker of whether you're achieving what you're looking to achieve?

DR. SOTO: Yes. We could develop a model in the phase 2 trial in ovarian cancer with CA 125, the marker that is widely used in ovarian cancer. And we could. In fact, for all this dose modulation that I have mentioned before, these PK/PD models were very useful not only for predicting neutropenia, is the main thing, but also we could develop models that define even PFS course, and we could have this impression of how the dose reduction was going to impact efficacy and

safety.

DR. GORLICK: My final question, in the Ewing sarcoma adult patient cohort, do you have a pre-existing bar for what you were going to define as efficacy? And do you have any sense of a historical control for what you would expect to see in that patient population?

DR. SOTO: Specifically in Ewing sarcoma?

DR. GORLICK: Yes.

DR. SOTO: We are using RECIST for the evaluation of tumor response, and for the moment, no. So again, as I said before, this is a huge basket trial with up to 300 patients.

This is something relatively new, that someone has said that the 18 percent is not very high, but I think that in other patients with some of them heavily pre-treated, I think it's meaningful. We have just discovered this quite recently, and we will start to learn how to measure all of these things specifically in this disease.

DR. RAETZ: Elizabeth Raetz, University of Utah. I just have a couple questions related to

the leukemia population. I was wondering what the rational was for a little different dosing schedule. It looks like the agent was dosed on days 1 and 8 in that population.

DR. SOTO: Yes, because it has been mentioned already in these ODAC meetings before, and it's so difficult to do phase 1 trials in acute leukemia because you don't have time, and especially because you are using single-agent drugs. You can seek something, but in general, these patients are -- the cancer is so aggressive that you don't have time to really evaluate the safety for deciding which will be the dose in this specific population, and the efficacy is very difficult to evaluate.

For example, in our trial, I think that we included about 50 patients, adults with acute leukemia. Finally, all of them were myeloid leukemia. And most of them were non-evaluable because they progress in 2 or 3 days, and we observed only 3 patients with some short-lasting, decreasing blasting bone marrow, so we decided to

stop.

The differences in schedules, we tried many things. As we couldn't deliver even two cycles, we said, okay, let's try day 1 and day 8, and after that, let's try day 1, day 2, and day 3 every something, but none of these strategies worked. Really, we stopped the development at least in that type of leukemia in adults.

DR. RAETZ: Then it might have been too early to tell because of the early failures, but just with the hematologic toxicity being a predominant toxicity that's been observed, in a hema malignancy population, did you see issues with infectious complications or unusual toxicity, or was it just too hard to tell?

DR. SOTO: Yes, sure. You are talking now specifically of the study in leukemia. Yes. The patients, most of them had to leave the treatment because they progressed very rapidly. But some of them with infections perhaps were even present when you studied very well, carefully, the clinical records, and you realize that really the patient

was included with something. And then, of course, lurbinectedin didn't help to protect the patient against infections.

DR. DuBOIS: Two follow-up questions. Related to Dr. Gorlick's question about pharmacodynamic markers, it seems to me that the Ewing's cohort in adults is a nice opportunity to validate the preclinical data that you shared related to the degradation of EWS-FLI. And I wonder if you have paired biopsies embedded within that ongoing trial.

DR. SOTO: Paired biopsies at the beginning?

DR. DuBOIS: Paired pre- and post-treatment.

DR. SOTO: This is really very difficult. And, again, the specifics of that trial didn't allow us to be so exclusive. But we will consider, but sometimes it's difficult to get these type of aggressive studies approved. Sometimes the patients are reluctant to this sequential attention of biopsies. But of course, we will try when we start to work with specific sites dedicated to doing sarcoma, especially in children.

DR. DuBOIS: You mentioned in the briefing book a combination trial with olaparib, which is another agent of interest in Ewing sarcoma. Are you able to share any data about how that trial is going?

DR. SOTO: Yes. This is also a trial that is not sponsored by Pharma Mar. But what I know is that the trial has completed, the phase 1 part. We have the right dose for the combination, and the phase 2, where we will check really the efficacy, has just started a few weeks ago.

DR. DuBOIS: [Inaudible - off mic].

DR. SOTO: Yes, many no volume, and some other indications.

DR. MacDONALD: Tobey MacDonald, Emory University. It appears from the data that your best responses are in tumors that express oncogenic drivers. For the pediatric trial, do you plan to capture the molecular information? Because it could be that it's not histologically specific, but more molecularly specific in terms of response.

DR. SOTO: Yes, we will try. In all the

patients that we can obtain a biopsy, we will do that.

DR. ARNDT: I'm just curious, in the combination studies of doxorubicin and this agent, what was the dose of doxorubicin?

DR. SOTO: Initially 50 and finally 40 milligrams per square meter.

DR. MORROW: You mentioned concerns about dose delay and dose reduction, so I just wanted to ask, in your complete responses, partial responses, et cetera, did you see any correlation with the dose of either your drug or the concomitant medication in terms of depth or duration response?

DR. SOTO: We have all the characteristics here, so we have patients that were very long-lasting responses that were treated with an initial lurbinectedin dose, in cases where we reduced the dose, and still the efficacy was there; and as I mentioned before, cases where we had to stop.

For example, we stopped development not only in doxo because of the cumulative toxicity but also in the paclitaxel combination study. And then we

continued with lurbinectedin alone, and there were a significant number of patients that still remained in response.

DR. MORROW: And with your CNS response, was that monotherapy or combo therapy?

DR. SOTO: Combo with doxo.

MS. PREUSSE: Courtney Preusse, Fred Hutch. Under potential challenges, you list liver maturation, and paclitaxel, cisplatin, and irinotecan in the literature show adverse effects on the liver, liver damage that is suspected to be associated with chemo administration.

So I'm curious, in a pediatric patient population, where I assume liver maturation means that the liver is still maturing until adulthood, how do you proposed to address that in combination therapy?

DR. SOTO: Initially, we will start with not so young children, so we will start from older than 2 years. And we will incorporate the information that we will obtain in PBPK models, physiological base pharmacokinetic models. And we'll have a lot

of information in around 2-year-old children, and then we'll try to be very conservative, taking this into account that, of course, children lower than 2 years can have more problems regarding the liver toxicity. Not only that, but also in the metabolism of the drug, that can put the kid at risk, for example, other toxicities, not only the liver.

DR. REAMAN: Just a couple of questions. You mentioned the proposed adult Ewing studies with the combination of lurbinectedin and irinotecan. Do you have plans to enroll patients below the age of 18 on that study?

DR. SOTO: This study will be conducted in the U.S., and we will include patients up to 16, so from 16 -- from 16. Sorry.

DR. REAMAN: Is there a reason for 16? We would encourage the enrollment of adolescents on appropriate disease-focused or targeted therapy trials. When the disease occurs in both the pediatric and adult populations, our experience is that the PK in 12 to 18-year-olds of many agents,

and including some classical cytotoxic agents, is no different than the adult population. So this may be one way of getting some early experience in the population that's most at risk for developing this disease.

DR. SOTO: Our understanding is that we should first test the drug single agent in children and then to try combinations. But if you really recommend us to go directly to a combination in children or in the pediatric population, this is something that can be considered.

We thought that the other way was more rational, but if you have experience, you have examples of cases where the investigations in children started with combination, we could consider it.

DR. REAMAN: It's clearly safer. There's plenty of pediatric and specifically adolescent experience with irinotecan. There's not with lurbinectedin, but you've provided single-agent toxicity data, which doesn't look outrageous. So it would be something to consider as you move

forward.

DR. SOTO: So as I said before, we are discussing right now the design of this combination trial, so we will incorporate this in the discussion.

DR. REAMAN: In that trial, there was the question before about possibly looking at serial biopsies. And I know that's problematic. It's particularly problematic in the pediatric population. But would you consider looking at circulating tumor cells or circulating free-tumor DNA as a way to evaluate efficacy, particularly in Ewing's?

DR. SOTO: In this trial, we will try to obtain the second biopsy to check -- to be sure of the rationale, we have to start trying -- this combination works in the patient. And the issue regarding CTC and circulating DNA, sometimes we have considered -- we from time to time discuss the convenience of a study in this arena, but the attempts that we have made were complex to implement in reality.

DR. REAMAN: Then one other question. This is a naturally occurring product. So what is the thought about the potential role of multi-drug resistance and particularly as you start looking in phase 2 for efficacy signals in previously heavily pre-treated patients that have multiple natural agents?

DR. SOTO: What we know is that the drug is very active after platinum, which is sometimes very challenging for many drugs. So this drug is a substrate of P-gp, and this can be one of the mechanisms of resistance.

If there is gross resistance in the regard you have mentioned, it could be, but even that this can be a possibility, we think that the activity that we are observing in heavily pre-treated patients is indicating that perhaps this mechanism is not acting at least at a high level.

DR. REAMAN: Thanks.

DR. WEIGEL: Brenda Weigel, University of Minnesota. I just want to comment a little bit on the very young patients. And I appreciate the

caution in going into the very young patients. Typically in a relapse setting, it is going to be incredibly unusual to have a patient much under 2. You may get an odd patient in the 1- to 2-year range. It's almost unheard of to have a patient in the relapsed clinical trial setting less than a year of age.

So to commit to an investigational plan that would mandate studying those very young children in any large numbers is actually not really a feasible thing to do. And an approach that has worked in some studies is once you establish a recommended dose or a safe dose level, allow enrollment with very, very careful safety monitoring of children kind of 6 months and over.

The liver metabolism issues are really an issue of the very, very young children, the really small neonates. By about 6 months if you're doing meter-squared dosing, you're pretty okay, and you build in very careful hepatotoxicity monitoring for that patient population. I think then you allow yourself to collect some of that very important

data should a patient like that arise, however, not being bound to studying it in any way, shape, or form with large patient numbers because they just don't exist.

But I think it's very reasonable to be cautious, but I wouldn't suggest making specific plans to separately study those patients, and certainly wouldn't think of a different dosing schedule or regimen for those patients.

DR. SOTO: Thank you.

DR. PAPPO: Any additional questions? Brenda?

DR. WEIGEL: I'm going to completely switch gears now and talk a little bit about optimization of the agent. You alluded to some solubility concerns, some delivery concerns of volume. What is your timeline for the development of optimization of some of those issues, and do you think that will be rate-limiting in any way?

DR. SOTO: We are working on that. We can't say when we will finish, but we are working now on the improvement of the formulation for trying to

work out it to children. But we have not defined timelines yet.

DR. TESH: Any additional questions, Alberto?

DR. REAMAN: Just to follow up on that, do you see having that optimization of the intravenous formulation completed before you start pediatric studies?

DR. SOTO: No, because as we will establish relatively big, we think before 2 years of age, we can have problems in this regard, but if more than 2 years, probably this is not going to be so relevant. So we are not going to wait until we have this optimization.

DR. REAMAN: Thanks.

MS. LUDWINSKI: Donna Ludwinski. I had a quick question about your phase 1 that's in combination with irinotecan. It looks like it only began a year ago, so possibly not that many patients have enrolled, but the tumor types that are listed there, it looks like Ewing sarcoma would be included. But I was just curious because the

trial does not allow prior treatment with irinotecan and topotecan.

What are you going to learn from that in the relapse setting if many of these tumor types are treated with that up front?

DR. SOTO: We have two trials in combination with irinotecan. The first one is ongoing, and we are very close to define the recommended dose. And even after that, after we have the recommended dose with initial dose escalation schedule, we will try to change the order of this escalation because in the beginning, we fixed the irinotecan dose, and we started to increase the lurbinectedin dose. But now that we have the recommended dose with this escalation method, we will change, and we will fix the lurbinectedin dose, and we'll start from very low doses of irinotecan.

This trial is open for many, many tumor types. For example -- and we have had good activity in some of them. And we will use this information to better plan the trial that I mentioned before, more oriented to the Ewing

sarcoma population.

DR. PAPPO: Any questions?

(No response.)

Questions to the Subcommittee and Discussion

DR. PAPPO: Thank you very much. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. We will start with the first question.

DR. KRAUSS: Please discuss the preliminary pediatric development plan, including the tumor type proposed for further study. In addition, please include considerations regarding a targeted approach based on bio or other markers versus one that's broader in scope.

DR. MASCARENHAS: There's data lacking here other than with Ewing sarcoma, and I would encourage generation of more preclinical data with regards to pediatric-specific tumors.

DR. PAPPO: I forgot to say there's no OPH.

I'm sorry. Steve?

DR. DuBOIS: My concern about the design is that it calls for essentially a second phase 2 study in, quote, "pediatric Ewing sarcoma" as a monotherapy experience. You already will have completed a, quote, "adult Ewing sarcoma phase 2," and I'm not sure I see the value in a second phase 2 of the exact same regimen in what I think most of us view as the exact same disease, whether the patient happens to be above or below 18 years of age.

So that would be my concern about, in a very rare disease, essentially duplicating a trial.

DR. PAPPO: Tobey?

DR. MacDONALD: I would just like to reiterate that I would strongly recommend doing some sort of tumor and/or germline sequencing panels to address what Leo was talking about in terms of are there histologies versus molecular profiles that more readily will respond to this drug.

DR. GORLICK: Richard Gorlick. It's clear

that this class of drug, meaning trabectedin versus lurbinectedin, has activity in malignancies. I think the issue is really understanding, from the mechanism of action, whether this is sort of a non-specific cytotoxic or it's a targeted agent to things with specific transcription-factored arrangements.

Then from there, starting to understand if it's targeting specific translocations, which seem to be the case for trabectedin, really, what's the spectrum of what defines activity and not. Certainly, if you're going to perform a study in the context of Ewing sarcoma, you're going to have to tighten up your definition of what Ewing sarcoma is.

In the field, active areas of debate are things like Ewing-like sarcomas. And the question is really, do we think this is going to affect the sort of P-COR [ph] or the CIC ducts for translocations associated with Ewing-like sarcoma., or is this specifically going to be EWS-FLI?

If we go beyond that as a statement, in

pediatrics, there are things like synovial sarcoma in the non-rhabdo soft-tissue sarcoma group. And you can imagine including the SYT-SSX translocation-associated if you believe in aberrant translocation factor drives it.

That starts the discussion if this is transcription-factor driven. Obviously, there are translocations driving transcription factors in the context of malignancies other than sarcoma. If you believe it's just the cytotoxic, then obviously that sort of opens the door to everything that isn't associated with recurrent translocation, but it's kind of understanding the biology of what drives activity. That should bound the scope of it.

I would not be overly influenced by efficacy in the context of an adult Ewing sarcoma trial. And I think some of the question is, really, we know Ewing sarcoma is a chemo-responsive disease. If there was a mixture of sarcomas that were less chemo-responsive, then the reason they may be seeing activity in the subgroup is just reflecting

the general chemosensitivity of this as a histologic subtype.

So I think they need to think more broadly about what groups this drug may work against and what tumor types should be included.

DR. PAPPO: Any additional questions or comments? Carola?

DR. ARNDT: I guess I'd also think about, echoing what Steve said, doing another study in a Ewing's patient population as a single agent and how are we going to use this drug going forward. Is it really only going to be used as a single agent? Doubt it. So why not do this drug in combination with something else?

I'm a little bit concerned that the dose of doxorubicin that was used in the studies was only 40 per meter squared, whereas we're used to using 75 milligrams per meter squared. So single agent versus multi-agent is something that should be considered.

DR. PAPPO: Any other questions or comments?

(No response.)

DR. PAPPO: So I'm going to try to summarize this. I think that it's important to get a broader spectrum of preclinical data. My own opinion would be, why are we choosing neuroblastoma? For example, there's absolutely zero evidence that was provided to us. And like Steve said earlier, there was no data provided of any kind of MYC-driven adult tumors to substantiate the use of this drug in neuroblastoma.

Number two, to be very, very thoughtful as to how you want to design another pediatric trial in Ewing's because, pretty much, you currently have an ongoing trial that is demonstrating some efficacy. I think that it will be interesting to note, to sort out which are the responders.

So I think that in future studies, it will be very important to either restrict enrollment of patients with a known translocation or to be sure that there is molecular data on all of these patients, so retrospectively you can say these are the patients that responded or not. That would be like a proof of principle that, indeed, this

activation of transcription factors is responsible for the response to the drug.

The other thing that has been said repeatedly is, is it worthwhile to continue to explore single-agent activity. And the other issue that was brought up earlier in the question and answer session to the sponsor was, there is already evidence that there is activity with irinotecan and this agent, and it would be worthwhile considering lowering the age enrollment for these patients to 12 or higher.

Did I miss anything or anything else I should add? Yes?

DR. DuBOIS: Just that the latter approach of extending an adult trial down to age 12 in combination with irinotecan does not necessarily preclude the need for a monotherapy pediatric trial in a broader set of indications and a broader set of pediatric ages.

DR. PAPPO: Correct. Thank you.

We will now proceed with question number 2.

DR. KRAUSS: Given the mechanism of action

of lurbinectedin, please consider other pediatric tumor types for which there is a biologic rationale for evaluation of its activity. Address any differences in biology between adult and pediatric hematologic malignancies that might support its evaluation of pediatric diseases for which its activity in adults has been limited.

DR. MASCARENHAS: I think Richard Gorlick discussed this with the previous question, really looking at translocation-driven malignancies potentially in a variety of sarcomas. In hematologic malignancies, I don't know I saw any data nor any rationale -- even with comparison to what is known about trabectedin, that there would be any rationale to study.

DR. RAETZ: Elizabeth Raetz. I think in the hema malignancy, one of the challenges is there really hasn't been successful trials with a single agent. And I think that's been the experience that's been observed so far in adults.

So I think, just as a similar theme, that combination studies would probably need to be

designed preclinically and would potentially run into the issue of overlapping hematologic toxicity. So there may be some challenges there, so maybe even perhaps combinations with other targeted agents could be considered if you wanted to move this forward in the hema malignancy space.

DR. DuBOIS: I think a potentially interesting clinical and scientific question may be whether some of the findings observed to date, both in the laboratory and in the clinical in Ewing sarcoma, might translate to other EWS-R1 translocated tumors such as clear-cell sarcoma or desmoplastic's Moran cell tumor.

So the sponsor might consider how to evaluate those other diseases that remain areas of significant unmet medical need.

DR. GORLICK: So it's a little tangential to how the question is phrased, but I think what has to be considered as well is the schedule of administration of this particular drug. I think there is data suggesting it's the peak dose of trabectedin that defines activity, but that would

be unusual for something that inhibits transcription. So as a class effect, you would expect the duration of exposure.

Clearly, the question -- big difference between these two agents, meaning trabectedin and this, is the biological half-life in the achievable peak dose. I think they need to think about investigating why that is.

DR. PAPPO: Any additional questions or comments?

(No response.)

DR. PAPPO: I will try to summarize this discussion. So something that has been previously said is to investigate is the response of this agent really translocation driven or not. It is also suggested that the sponsor investigate other histologies that have a fusion; for example, synovial sarcoma or other histologies that have EWS-FLI infusions like clear-cell sarcoma and desmoplastic's Moran cell tumor.

Also, it will be important to better determine what is the optimal schedule of

administration given the presumptive mechanism of action that has been presented. Then as it relates to leukemia, we strongly recommend that there should be a trial with a combination therapy and perhaps even using targeted agents coupled with this drug to assess the efficacy of this agent in recurrent leukemia.

Anything else?

DR. DuBOIS: Did we strongly recommend a leukemia trial?

DR. PAPPO: We did not, but if you're going to pursue that --

DR. DuBOIS: If you're going to pursue a trial --

DR. PAPPO: Yes. This has to be --

DR. DuBOIS: -- do it in combination. Fine.

DR. PAPPO: No, no. I'm not saying that we should do it.

DR. DuBOIS: Okay. Fine.

DR. PAPPO: If you're going to pursue a clinical trial in leukemia, you should -- sorry.

Anything else I missed?

DR. REAMAN: No. One other tumor that we might want to think about is rhabdo, alveolar rhabdo.

DR. PAPPO: Right, of course.

DR. REAMAN: It's certainly much more common.

DR. PAPPO: 213, 113.

DR. REAMAN: We've discussed the paucity of targeted drugs for pediatric tumors because of the lack of development of agents for specific fusion protein.

So this might be an opportunity to actually do a basket trial or some master protocol that is specifically evaluating translocations and specific fusions, irrespective of histology, look. And then you would have some more biological information to provide a real direction as far as development in the pediatric age group.

DR. PAPPO: There was actually a specific trial for translocation-positive sarcomas. So perhaps something similar to that, if you believe that that's the driving mechanism, is something

that you would investigate.

DR. MacDONALD: I'd just add, prior to a trial, it's relatively straightforward to just do a preclinical drug screen using multiple cell lines with a variety of translocations and/or aberrations that drive transcription to get quickly at some of those targets.

DR. MASCARENHAS: Given the potential proposed mechanism of action, whether we believe it or not, others downstream targets of EWS-FLI1 agents could be explored in preclinical data, for example, POP 1 inhibition, together with this agent.

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

DR. KRAUSS: Please discuss the impact of low CNS in testicular penetration of lurbinectedin in tissue distribution studies and potential areas of study in the pediatric population.

DR. MASCARENHAS: I think the only relevance is for hematologic malignancies, so that should be taken into consideration.

DR. WEIGEL: I think the statements were made, but I'm not sure that we have compelling evidence towards a lack of CNS penetration, given there's been a documented response and it's a disrupted blood-brain barrier. I think it's pretty controversial. And I'm not sure what low means.

DR. PAPPO: Any other comments? Greg?

DR. REAMAN: So would there be a particular interest in evaluating this in a primary CNS tumor setting, I think was part of the thinking behind this, probably more than the metastatic tumor setting.

DR. WEIGEL: I guess I would say that would get back to some of the comments Tobey's made, and based on the biology, and then being able to look at preclinical studies to ascertain whether that would be something worth investigating. But I think if the preclinical data supported it, I'm not sure we were provided with evidence to say that we shouldn't study it.

DR. REAMAN: Right.

DR. PAPPO: Any other comments or questions

regarding this question?

(No response.)

DR. PAPPO: So I'm going to try to summarize this. On the one hand, the relatively low penetration in the CNS and testicle might be an issue for hematologic malignancies. However, we already heard from the presentation that there was a patient that had a response in the setting of CNS disease.

So we need to better clarify really what low means and perhaps if in a screen there is a potential for using this drug within the setting of CNS tumors, that should be considered.

Any additional?

(No response.)

DR. PAPPO: We'll move to question number 4.

DR. KRAUSS: Please address any potential safety concerns unique to the pediatric population, including consideration as to whether any pediatric age groups should be excluded from study.

DR. WEIGEL: I think the data was presented very clearly for the single agent, that this is

really a myelotoxic drug. One of the concerns I have that I would encourage very thoughtful consideration is there's quite variable PK. Dr. Gorlick has mentioned that it may be the peak, but also based biologically, we want to see an extended exposure.

The comments were made that about 40 percent of patients require a dose reduction to sustain dosing of this agent as a single agent, and that may be very important information to do extended cycle PKs, to really understand the use of the agent.

I also think very careful attention needs to be paid to understanding the pharmacokinetics and exposures of combinations. And I do not think that we necessarily should exclude particular patients. However, I think we need to really design those studies to learn as much information as possible about the drug metabolism and exposures required to get the desired effects.

DR. DuBOIS: I missed the concern about the drug formulation here. In the briefing book,

there's mention of concern of the volume, the fixed volume of 100 mLs, but administered over 1 hour even to a 10-kilogram baby, which would be the average weight of a 12-month-old, that's not a clinical concern from my perspective.

There's mention of lactate in the product, and I would think maybe if there's enough of that in a very small infant, that that could potentially lead to issues with metabolic acidosis, but that would have to be a very large amount of lactate.

So in terms of the formulation issues, I didn't have particular concerns, given that the initial age proposed was going to be 2 years and up anyway.

DR. REAMAN: I think the real reason for this question was to generate the discussion that we've actually already had about the concern and the over- perhaps protective stance of enrolling patients after 2 years of age when we don't see any real physiologic reason for doing so.

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

(No response.)

DR. PAPPO: If I could summarize this, the data presented on toxicity was very well presented. It appears that the main toxicity is myelotoxicity and also transaminase, transaminitis. It's important to explore different schedules and to better delineate the PK of this agent with extended exposure studies, since approximately 40 percent of the patients with single agent had to have a dose reduction with this agent.

There were no significant concerns regarding the formulation. And the amount of fluid that needs to be mixed with 100 mLs is really not a concern in the age population that we're going to be studying.

I think that that's the main things. Did I miss anything?

MS. PREUSSE: One comment. Without additional data on the AEs, adverse events -- further studies really need to elucidate what those AEs are with this drug in combination with others.

DR. PAPPO: So for the characterization of adverse events in combination with other agents that potentially would be used to treat pediatric cancers. Anything else?

(No response.)

Adjournment

DR. PAPPO: We will now break for lunch, and we will reconvene in this room at 1:10, 10 minutes past 1:00. Panel members, please remember that there should be no discussion of the meeting topic during lunch, among yourselves, or with any other member of the audience. Thank you very much.

(Whereupon, at 11:47 a.m., the session was adjourned.)