FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE(pedsODAC)

Wednesday, June 17, 2020

10:00 a.m. to 12:05 p.m.

Topic 1

Morning Session

Virtual Meeting

Meeting Roster

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Consultant Management

Office of Executive Programs, CDER, FDA

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(Consumer Representative)

(Participation in Day 1 Topic 1 and Day 2 Only)

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(10:00 a.m.)

Call to Order

Introduction of Committee

DR. PAPPO: Good morning. First of all, I would like to thank Dr. LaToya Bonner and all of the very talented staff of the FDA for organizing this virtual meeting and for taking the time to let the panel become familiar with Adobe Connect. We truly appreciate all your efforts to allow us to help navigate this app and also to become familiar with it and try to make this meeting run as smoothly as possible.

Good morning and welcome. For media and press, I would like to announce the FDA press contact is Nathan Arnold. His email is nathan.arnold@fda.hhs.gov, and his phone number is 301-796-6248. My name is Alberto Pappo, and I will be chairing today's virtual meeting. I will now call the morning session of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee to order. We will start by going down

the meeting roster and introducing ourselves.

We will use a call/respond method, and we think that this will work better. I will call the panel member's name to prompt the member to speak, and then we will ask the panel members to introduce themselves into the record. We will start with David Mitchell.

(No response.)

DR. PAPPO: We will then go to --

MR. MITCHELL: Dr. Pappo, I'm sorry. I had to unmute myself. I'm David Mitchell. I'm a consumer representative, but more importantly, I'm a cancer patient. I have multiple myeloma and in continuous treatment, and have been for almost 10 years.

DR. PAPPO: Thank you. My name is Alberto Pappo. I'm the chairperson of the pedsODAC. I'm a pediatric oncologist, and I work at St. Jude.

Dr. Jonathan Cheng?

DR. CHENG: Good morning. Jonathan Cheng. I'm the industry rep, and I'm with Merck Pharmaceuticals.

DR. PAPPO: Dr. Catherine Bollard?

DR. BOLLARD: Hi. This is Dr. Catherine Bollard. I'm the director for the Center for Cancer and Immunology Research at Children's National and at George Washington University here in Washington, DC.

DR. PAPPO: Dr. Ira Dunkel?

DR. DUNKEL: Good morning. My name is Ira Dunkel. I'm a pediatric neuro-oncologist at Memorial Sloan Kettering Cancer Center in New York City.

DR. PAPPO: Dr. Julia Glade Bender?

DR. GLADE BENDER: Good morning. My name is Julia Glade Bender. I'm also at the Memorial Sloan Kettering Cancer Center in New York City, where I serve as the vice chair for clinical research in the Department of Pediatrics.

DR. PAPPO: Dr. Richard Gorlick?

DR. GORLICK: Good morning, everybody. I'm Richard Gorlick. I am the division head of pediatrics at MD Anderson Cancer Center in Houston, Texas.

DR. PAPPO: Dr. Theodore Laetsch?

DR. LAETSCH: Good morning. I'm Theodore Laetsch. I'm a pediatric oncologist at UT Southwestern Medical Center in Dallas.

DR. PAPPO: Donna Ludwinski?

MS. LUDWINSKI: Good morning, Donna Ludwinski from Solving Kids' Cancer in New York.

DR. PAPPO: Dr. Andy Kolb?

DR. KOLB: Good morning. This is Andy Kolb. I'm a director of the Nemours Center for Cancer and Blood Disorders at Nemours/Alfred I. duPont Hospital for Children in Delaware.

DR. PAPPO: Dr. Katherine Janeway?

DR. JANEWAY: Good morning. I'm Katie Janeway. I'm a pediatric oncologist and sarcoma expert at Dana-Farber and Boston Children's Hospital in Boston, Massachusetts.

DR. PAPPO: Dr. Naynesh Kamani?

(No response.)

DR. PAPPO: Dr. Kamani, if you can hear us, can you introduce yourself for the record?

DR. KAMANI: Good morning. Can you hear me?

DR. PAPPO: Yes.

DR. KAMANI: Hi. Good morning. I'm Naynesh Kamani, pediatric immunologist and bone marrow transplanter at Children's National Hospital, Washington, DC and at George Washington University.

DR. PAPPO: Dr. Tobey MacDonald?

DR. MacDONALD: Good morning. This is Tobey MacDonald. I'm director of pediatric neuro-oncology at Emory University and Children's Healthcare of Atlanta.

DR. PAPPO: Dr. Leo Mascarenhas?

DR. MASCARENHAS: Good morning. I'm Leo Mascarenhas, the deputy director of the Cancer and Blood Disease Institute at Children's Hospital Los Angeles, where I also serve as the head of oncology.

DR. PAPPO: Dr. William Parsons?

DR. PARSONS: Hi. This is Will Parsons. I'm a pediatric oncologist and deputy director of Texas Children's Cancer and Hematology Centers at Baylor College of Medicine in Houston, Texas.

DR. PAPPO: Dr. Elizabeth Raetz?

DR. RAETZ: Good morning. This is Elizabeth Raetz. I'm a pediatric oncologist and division director at New York University.

DR. PAPPO: Dr. Nita Seibel?

DR. SEIBEL: Hi. This is Nita Seibel. I'm a pediatric oncologist in the clinical investigations branch of CTEP at the National Cancer Institute.

DR. PAPPO: Dr. Malcolm Smith?

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

DR. PAPPO: Do we have more slides or are we done with the slides?

(No response.)

DR. PAPPO: Can we have the next slide?

Dr. LaToya Bonner?

CDR BONNER: Good morning. This is LaToya. I am the DFO for this meeting.

DR. PAPPO: Dr. Greg Reaman?

DR. REAMAN: Good morning. This is Gregory

Reaman. I'm the associate director for pediatric oncology in the FDA's Oncology Center of Excellence.

DR. PAPPO: Dr. Denise Casey?

DR. CASEY: Hi. Good morning. This is Denise Casey. I am a pediatric oncologist and acting team lead for sarcoma melanoma at FDA.

DR. PAPPO: Do we have any additional slides?

(No response.)

DR. PAPPO: I think that's pretty much -- well, I think we need a Dr. Leslie Doros. Do we have a picture of her on the next slide?

DR. DOROS: Well, if we don't, hello. This is Leslie Doros. I'm a pediatric oncologist at the FDA in the Division of Oncology 3.

DR. PAPPO: Also Christine Lincoln from the FDA?

MS. LINCOLN: Hi. I'm an attendant as well, and I don't have a picture.

DR. PAPPO: Okay. I think that's pretty much everybody.

Did I leave anybody out, and would you like to introduce yourselves for the record?

(No response.)

DR. PAPPO: Okay. We will proceed then.

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 gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

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

We are aware that members of the media are anxious to speak with the FDA about these

proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

We will proceed with the FDA introductory remarks from Dr. Greg Reaman.

Introductory Remarks - Gregory Reaman

DR. REAMAN: Good morning. I just want to also extend a welcome to the advisors and to our pharma company sponsors for this virtual meeting of the Pediatric Subcommittee of ODAC. This is the first, and I appreciate your flexibility.

As in the past, our focus at this meeting is to accelerate the timely development of novel anticancer agents with potential applicability to pediatric cancers. At present, the only legislative initiative relevant to pediatric cancer drug development is the Best Pharmaceuticals for Children Act.

We will hear presentations and discuss two products in early development under investigational

new drug applications in an attempt to maximize the agency's authority under BPCA, which is a voluntary program. Those products are SP-2577, seclidemstat, the epigenetic modifier from Salarius, and marizomib, a proteosome inhibitor from Bristol-Myers Squibb.

The company presentations and expert panel discussions and recommendations will serve to help inform the review divisions of the Office of Oncologic Diseases and the Office of Tissue and Advanced Therapies in the Center for Biologics and the Oncology Center of Excellence as to whether written request for pediatric assessment should be issued for these products based on the degree of unmet clinical need and the potential public health benefit to children; the extent of nonclinical data and clinical data in adults to warrant and support pediatric investigations; and a review of the benefit-risk considerations.

So again, I would like to thank you for your service to the committee and your service to the agency. Thank you.

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

Dr. LaToya Bonner will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

CDR BONNER: Good morning. The Food and Drug Administration is convening today's meeting of the Pediatric Oncology Subcommittee of the Oncologic Drug Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the industry representative, all members of the committee and temporary voting members of the subcommittee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

of the committee and temporary voting members of the subcommittee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs 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 discussions of today's meeting, members of the committee and temporary voting members of the subcommittee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for the 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.

For today's agenda, information will be presented regarding pediatric development plans for two products that are in the development for an oncology indication. The subcommittee will consider and discuss issues relating to the development of each product for pediatric use and provide guidance to facilitate the formulation of written requests for pediatric studies if appropriate. The product under consideration for this session is SP-2577, presentation by Salarius Pharmaceuticals, Incorporated.

This is a particular matters meeting during which specific matters related to SP-2577 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. Ira Dunkel, Julia Glade Bender, Richard Gorlick, Theodore Laetsch, and Leo Mascarenhas.

Dr. Dunkel's waiver involves consulting interest with three companies for which he received remuneration between $0 to $5,000 per year from two companies and between $10,001 and $25,000 per year from a third company.

Dr. Glade Bender's waiver involves her employer's contract for a study of SP-2577 funded by Salarius Pharmaceuticals.

Dr. Gorlick's waiver involves his employer's contract for a study of SP-2577 sponsored by Salarius Pharmaceuticals and funded by the National Pediatric Cancer Foundation.

Dr. Laetsch's waiver involves three of his employer's research contracts. One is funded by the Children's Oncology Group; the second is funded by the Neuroblastoma and Medulloblastoma Translational Research Consortium; and the third is funded by Eisai.

Dr. Mascarenhas' waiver involves two of his employer's research contracts. One is a study of

SP-2577 sponsored by Salarius Pharmaceuticals and funded by the National Pediatric Cancer Foundation, and the other is a study funded by AstraZeneca.

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 at http://www.fda.gov/advisorycommittees/committeesmeetingmaterials/drugs/default.htm.

Copies of the waivers may be obtained by submitting a written request to the agency's Freedom of Information division. The address is 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267. For the record, Dr. Steven DuBois has self-recused from participating in this session of the meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statement that they have made concerning the product at issue. With respect to FDA's invited industry representative,

we would like to disclose that Dr. Jonathan Cheng is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Cheng's role at this meeting is to represent industry in general and not any particular company. Dr. Cheng is employed by Merck.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the subcommittee of any financial relationships that they may have with the firm at issue. Thank you.

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

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To

ensure such transparency at the advisory committee meeting, FDA believes that it's important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicants 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 interest 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 Salarius Pharmaceuticals' presentation.

(Pause.)

DR. PAPPO: Are we able to start the presentation?

CAPT WAPLES: Hi. Good morning, sir. We are working on it.

MR. ARTHUR: This is David Arthur, CEO of Salarius. We prerecorded the presentation and submitted it. I believe we're looking for the committee to begin the recording.

CAPT WAPLES: Yes, sir. That is correct. We're working on bringing that up.

(Pause.)

[Salarius recording played.]

Industry Presentation - David Arthur

MR. ARTHUR: Good morning. I'm David Arthur, CEO of Salarius Pharmaceuticals, and on behalf of the entire Salarius team, I'd like to thank the committee for inviting us to review the seclidemstat development plan. We are looking forward to today's discussion. Joining me today as presenters are Dr. Bruce McCreedy, chief scientific officer; Dr. Damon Reed, principal investigator of our ongoing Ewing sarcoma clinical trial; and Dr.

Margaret Dugan, senior medical advisor.

Over the past few years, we have achieved several development milestones, including orphan drug designation; rare pediatric disease designation; IND activation; initial enrollment in both of our ongoing clinical trials; and most recently in December of last year, fast-track designation. These milestones all support the ongoing development of seclidemstat for the treatment of relapsed or refractory Ewing's sarcoma.

Why are we here? As every member of the committee knows, Ewing sarcoma is a devastating disease predominantly affecting children and young adults.

[Overlap of recording and live voice.]

MR. ARTHUR: This is David Arthur, CEO of Salarius. I do not believe [indiscernible] can hear the audio associated with the presentation.

DR. PAPPO: Correct.

[Salarius recording continued.]

MR. ARTHUR: Salarius is currently

completing dose escalation, and at this moment in time, input and feedback from the committee could be pivotal in the development of this potential new treatment for patients, patients that truly need new treatments the most.

We believe preclinical data supports pursuing a Ewing sarcoma indication, and as mentioned, we are completing dose escalation and will then begin dose expansion by treating a larger group of patients at the maximum tolerated dose. We are currently exploring potential tumor engagement and efficacy markers.

We are seeking committee feedback on how best to identify efficacy signals in our clinical program. The current study population is generally heavily pretreated with high tumor load, and unfortunately the patients are progressing.

We believe epigenetic therapies require time for epigenetic reprogramming, and we want to ensure that efficacy in this population is identified so that we can continue to quickly develop seclidemstat for these patients in need.

In addition, we would also like the committee's input on innovative trial designs that support the identification of efficacy signals and support the overall seclidemstat development program. Salarius is committed to developing seclidemstat for patients in need and look forward to the committee's input on how to optimize this process.

I'd like to now introduce Dr. Bruce McCreedy to review mechanism of action, our design rationale, and preclinical data.

Industry Presentation - Bruce McCreedy

DR. McCREEDY: Thank you, David.

Epigenetic enzymes represent attractive targets for cancer therapeutics given their role in regulation of gene expression. These enzymes can modify DNA and histones, resulting in changes to chromatin structure to a densely packed closed state which is non-permissive for transcription or to a relaxed open state, which is permissive for transcription.

In addition, many epigenetic enzymes

associate with repressive or activating protein complexes to affect regulation of gene expression. Overactivity of epigenetic enzymes can result in changes to the normal transcriptional balance and lead to cancer development and progression as a result of upregulation of genes associated with tumor growth and downregulation of tumor suppressor genes. Drugs that inhibit epigenetic enzyme activity can help treat cancer by reversing this regulation of gene expression and restoring a normal transcriptional state.

LSD1 is an epigenetic enzyme that affects gene transcription via its FAD-dependent enzymatic domain, demethylates mono, and dimethyl histone 3 lysine 4 and 9 [indiscernible], thereby modifying chromatin structure and access to transcriptional machinery.

In addition, LSD1 can affect repression and activation of transcription by interacting with various activating and repressive protein complexes via its tower domain. LSD1 activity is required for normal hematopoiesis, maintenance of stemness

and differentiation, as well as roles of cell motility, epithelial mesenchymal transition, and autophagy.

Overexpression of LSD1 is associated with tumorigenesis and disease progression as a result of both its enyzmatic histone demethylase activity and interactions with various transcriptional regulatory protein complexes. High levels of tumor associated with LSD1 expression is associated with a poor prognosis.

First generation LSD1 inhibitors bind irreversibly at a site in the catalytic domain and prevent binding of the required co-factor FAD. Although potent inhibition develops within enzymatic activity is achieved, these compounds are associated with hematologic toxicity, mostly neutropenia and thrombocytopenia.

In addition to first generation, irreversible inhibitors do not inhibit many of the scaffolding of protein-protein interaction between LSD1 and various transcriptional co-regulatory protein complexes.

Shown on the right, SP-2577, seclidemstat, is a first-in-class reversible inhibitor, an LSD1, that binds at a novel site within the enzymatic domain. This novel and reversible binding may explain why SP-2577 demonstrates more extensive inhibition of LSD1 scaffolding protein interaction, as well as the decreased risk of hematologic toxicity.

LSD1 can remove both transcriptionally permissive and repressive histone marks. The picture in the left panel of this slide with seclidemstat, like other LSD1 inhibitors currently in development, inhibits LSD1 demethylation of mono and dimethyl H3K9 to prevent the activation of previously silenced genes.

Inhibition of LSD1 enzymatic activity by seclidemstat in the PC3 prostate cancer cell results in increased repressive methyl marks on histone 3 lysine 9. However, due to its unique binding site and reversible binding, seclidemstat is also able to inhibit LSD1 scaffolding activity with DNA binding proteins and regulatory complexes

such as transcriptional co-regulators that are associated with oncogenesis.

Shown on the right side of the slide is seclidemstat's ability to inhibit association of LSD1 with the androgen receptor to prevent activation of androgen receptor target genes in the LNCaP prostate cancer cell line.

Ewing sarcoma is driven by a fusion oncoprotein that results from chromosomal translocation between EWS and ETS gene family members such as ERG and FLI1. In approximately 90 percent of cases, a t(1122) translocation results in production of EWS/FLI1 fusion oncoprotein. EWS/FLI1 fusion protein is a transcription factor that interacts with coactivators and corepressors that may also recruit LSD1 to drive the activation of tumor growth gene and deactivation of tumor suppressor gene. Ewing sarcoma cells highly express LSD1 and are dependent on LSD1 ne activity for survival.

Seclidemstat inhibits the growth of the Ewing sarcoma cells by disrupting LSD1 association

with co-activators and corepressors that act in concert with the EWS/FLI1 oncoprotein to promote transcriptional genes that are associated with oncogenesis or repress the expression of tumor suppressor genes.

Shown on the right side of this slide is the impact and treatment of A673 Ewing sarcoma cells with SP-2509. This was the first-generation compound that is structurally similar to SP-2577, seclidemstat. Cells are treated 2509 vehicle or control sh-RNA or an sh-RNA targeted EWS/FLI mRNA. As we can see from the heat map of upregulated and downregulated genes, treatment with SP-2509 results in the reversal of many up- and downregulated genes that are driven by EWS/FLI activity in much the same manner as a knock down of EWS/FLI protein level despite targeted sh-RNA.

The inset to the right of the heat map shows that A673 cells that highly express the EWS/FLI oncoprotein are more sensitive to growth inhibition by SP-2509 than are cells that show little or no expression of EWS/FLI protein. SP-2577 shows

antiproliferative activity against a panel of Ewing sarcoma cell lines with IC50 values ranging between 185 to 1269 nanomolars. In the SK-N-MC mouse xenograft model of Ewing sarcoma, SP-2577 shows potent tumor growth inhibition that results in a significant increase in survival and complete cures in 80 percent of treated animals.

Given seclidemstat's proposed mechanism of action in Ewing sarcoma, additional sarcomas are of interest for future clinical trials because they either share a similar translocation to EWS/FLI1 that interacts with LSD1 and/or has elevated LSD1 expression and are sensitive to LSD1 inhibition.

These sarcomas that affect pediatric populations include desmoplastic small round cell tumor, which often results in the translocation with EWS/WT1; myxoid liposarcoma, which includes translocations between EWS/CHOP as well as FUS/CHOP; as well as rhabdomyosarcoma and osteosarcoma, which display an increased level of LSD1 expression and rely on LSD1 activity for proliferation and colony formation.

Now, I'd like to introduce Dr. Damon Reed from the Moffitt Cancer Center.

Industry Presentation - Damon Reed

DR. REED: Thank you, Bruce.

I'm Damon Reed. I'm an associate professor and I'm the principal investigator for the seclidemstat phase 1 trial. Ewing sarcoma is relatively rare amongst cancer but very common in the pediatric age range with 400 new patients diagnosed every year with a median age firmly in the pediatric space of 15 years of age. Three quarters of patients present with localized disease and a quarter percent with metastatic disease.

All of these patients are treated with a standard of care up front of 29 weeks of chemotherapy, 35 inpatient days, and surgery or radiation for local control. These therapies can lead to cardiotoxicity, secondary cancer, and other morbidities.

There has been some improvement by intensifying therapy and adding more drugs with Ewing sarcoma over the decades but no improvement

to metastatic survival. Unfortunately, relapsed disease mirrors this poor survival curve shown in metastatic Ewing sarcoma on the next slide.

About a third of patients will relapse with their disease and they have a very poor outcome, less than 10 percent long-term survival. There are no FDA-approved agents for relapsed Ewing sarcoma, and this relapsed Ewing sarcoma is an area of unmet need with it being the third most common tumor enrolled on the pedi-MATCH trial, which is available for patients who don't have other clinical trial options.

So while there are relapsed regimens, there is no standard of care for relapsed Ewing sarcoma, and this table shows many of the regimens that are used. There is very little prospective evidence with much of this borrowed from single institution studies with few patients, and there's no published randomized evidence comparing these regimens. While there are responses in these relapsed regimens, complete responses are very rare.

It is in this context of poor standard of

care for relapsed Ewing sarcoma and poor outcomes that led to the phase 1 trial that we're conducting with seclidemstat as the first-in-human trial in Ewing sarcoma.

I'm proud that our phase 1 trial has correlates to advance the science of this disease as relapsed Ewing sarcoma is poorly understood, and these include cell-free DNA looking for digital droplet PCR for the Ewing sarcoma translocation and other novel technologies to look for a biomarker of tumor in the blood; circulating tumor cells as well to look for Ewing sarcoma cells, and other biomarkers such as lactate dehydrogenase, pharmacodynamic biomarkers like hemoglobin F concentrations which may arise with LSD1 inhibition; and in dose expansion, serial frozen biopsies required at screenings, cycle 2, and at the end of therapy to evaluate seclidemstat's effect and resistance.

In this rare relapsed population of Ewing sarcoma, a historical cohort should be considered with ongoing work to help with threshold setting

and event-free survival bars, such as presented by Dr. Angie Collier with the relapsed Children's Oncology Group phase 2 studies of 12 percent point estimate for 6-month EFS; and the ongoing rEECur trial that will add prospective evidence to this response rate could also be considered.

Now I'd like to introduce Dr. Margaret Dugan.

Industry Presentation - Margaret Dugan

DR. DUGAN: Thank you, Damon.

Good morning. I will be presenting an update on the early clinical program of seclidemstat in Ewing sarcoma. The first-in-human phase 1 study is being conducted in patients with relapsed refractory Ewing sarcoma.

As with all phase 1 studies, the primary objective is to evaluate the safety and tolerability of single-agent seclidemstat across multiple escalating doses, administered as a 75-milligram tablet strength in the fasted state as a BID dosing regimen given daily. Secondary objectives include determination of MTD;

characterization of PK; evaluation of the effect of food; and preliminary antitumor activity in these patients.

As Damon has previously stated, exploratory objectives include assessment of cell-free DNA, circulating tumor cells and tumor tissue for pharmacodynamic markers of disease burden, tumor response, and drug effect. Cell-free DNA will be analyzed to quantify the EWS/ETS translocations. Circulating tumor cells will be quantified and also assessed for gene expression profiles. Tumor biopsies will be assessed for genome-wide expression patterns, mutational profiles, as well as LSD1 protein levels.

Looking at the key study eligibility, patients must have a histologic diagnosis of Ewing sarcoma that is refractory or recurrent, including at least one prior course of therapy, which must have contained a camptothecin based regimen, or it was contraindicated, or the patient declined such treatment. Patients are at least 12 years of age and at least 40 kilograms in weight. Patients must

have a good performance status and radiographic evidence of measurable disease for dose-expansion patients.

This phase 1 study is enrolling on to seven dose-escalation steps starting at 75 milligrams to 1500 milligrams BID from eight U.S. sites. The study began with an accelerated dose-escalation design in which single patient cohorts were enrolled until a drug-related grade 2 or higher adverse event or a DLT was observed in cycle 1, at which point a classic 3-plus-3 design started enrolling at least three patient cohorts.

The dose escalation will stop upon observation of 2 DLTS during the first cycle in a cohort of 3 to 6 patients or when the 1500-milligram BID dose level has been determined to be safe. This will define either the maximum tolerated dose or the maximum acceptable dose; then at that dose, a total of 20 patients will be enrolled to further define the safety and preliminary antitumor activity of seclidemstat.

This study is currently enrolling onto

1200-milligram BID dose level. Of the 16 patients enrolled as of our data cutoff of December 2019, the median age was 25 years with 88 percent of patients being between 18 and 68 years old; 63 percent were male and 69 percent had good performance status, 90 or higher.

The majority of patients had surgery and/or radiation therapy; 81 percent had a prior camptothecin-containing regimen; 69 percent had received three or more prior regimens. All patients had a gene rearrangement of EWSR1 as per local assessment. Although not an entry requirement, the majority of patients had measurable disease at baseline.

Sites of metastases are typical for this patient population. The median time from initial diagnosis to study drug was 4.2 years with the majority of patients being two or more years from their initial diagnosis.

Overall, this patient population represents a heavily pretreated group of Ewing sarcoma patients. Cycle 1, single-dose pharmacokinetics

have been assessed in 13 evaluable patients treated at doses of 75 to 900 milligrams BID. Under fasting conditions, a proportional and linear increase in AUC and Cmax has been observed. The half-life is approximately 5 to 8 hours.

Using PK modeling at 900 milligrams BID, exposure is expected to be above 1000 nanograms per mL for approximately 16 to 20 hours per day, while at 1200 milligrams BID, exposure is expected to be above that level for the full day. 1000 nanograms per mL represents the expected efficacious concentration based on preclinical studies.

In conclusion, dose escalation continues at the highest doses to define the MTD or MAD, and at clear dose levels, seclidemstat is safe and tolerable. PK demonstrates dose proportionality with sustained exposure for up to 24 hours at these higher doses. The study population represents an advanced heavily pretreated group of Ewing sarcoma patients with extensive disease involvement who define an unmet medical need.

Seclidemstat is a novel, selective,

reversible LSD1 inhibitor developed to address this unmet medical need which selectively targets the underlying mechanism of disease to improve patient outcomes. Salarius continues its phase 1 studies with a commitment to the pediatric population and are seeking guidance on the appropriate studies for a proposed pediatric study request.

This concludes our presentation. We are happy to take your questions.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you very much. We will now take clarifying questions for Salarius Pharmaceuticals. Please use the raised-hand icon to indicate that you have a question. Please remember to put your hand down after you have asked your question, and please remember to state your name for the record before you speak. It would be helpful to acknowledge the end of your question with a thank you and end your follow-up question with a "that is all for my questions" so we can move on to the next panel.

I see Julia Glade Bender.

(No response.)

DR. PAPPO: Julia, would you like to ask a question?

DR. GLADE BENDER: Yes, please.

Good morning. This is Julia Glade Bender from Memorial Sloan Kettering. Thank you very much for the presentation this morning. I was wondering two things. The first question is, why was a prior camptothecin regimen required for study entry for the phase 1 trial? The second question is, if you could please review any preclinical data that you have using seclidemstat in combination with chemotherapy. Thank you.

DR. DUGAN: This is Margaret Dugan. I'm the senior medical advisor for Salarius, and I can take the first part of that question. At the time, this was a first-in-human, phase 1 study for patients with Ewing sarcoma, and it was felt that they must have had failed a standard-of-care therapy.

I'd like to ask Aundrietta to answer the second part of the question. Dr. Duncan?

DR. DUNCAN: Hi. This is Aundrietta Duncan,

associate director of nonclinical development. Thank you, Dr. Dugan.

We do have some preclinical data in combination with chemotherapy with seclidemstat. Those data were actually generated by Dr. Damon Reed who is on the call, so I would like to pass this question along to him.

DR. REED: Okay. Thank you very much, and excellent questions, both of them.

Technically, on this current trial, just to answer number one, camptothecin is not required, but a discussion regarding that is required. When we designed the trial, we wanted to make sure that patients at least knew of other therapies, so we kind of built that into the inclusion criteria. But technically at this moment and from the beginning of the trial, patients could have failed standard first-line therapy in Ewing sarcoma and gone directly to seclidemstat, but so far that has not occurred.

In terms of the preclinical, the second question, we have studied in vitro across multiple

cell lines in Ewing sarcoma, and we do this guided by a paper from 2013 that suggests using clinically achievable doses and the presence of protein concentrations that reflect protein binding, and for durations of exposure that would match the human PK.

While we didn't have that for seclidemstat, we did test this agent along with some others and, in general, seclidemstat both combined well with synergy or additive effects across a broad spectrum of different traditionally used therapies like SN-38, the derivative of irinotecan and topotecan, or 4-HC, a cyclophosphamide derivative, or etoposide. So in general, seclidemstat shows promising in vitro combination activity in Ewing's sarcoma cell lines.

DR. GLADE BENDER: Thank you. That's all my questions.

DR. PAPPO: Next is Dr. Katie Janeway.

DR. JANEWAY: Yes. I would like to thank the presenters for the very informative presentation. I am wondering if you are able to

share any information about toxicity at this point. Thank you.

DR. DUGAN: Yes. Thank you. This is Margaret Dugan. The current safety profile does not define any prohibitive toxicity, and there are no treatment-related study discontinuations or deaths. The overall frequency of treatment-emergent adverse events related to seclidemstat of grade 3 or 4 is very low. We have seen one DLT of nausea, vomiting, and abdominal pain judged to be treatment related, and the trial continues in its dose-escalation phase at the 1200-milligram dose.

DR. JANEWAY: This is Katie Janeway with just one follow-up question. Are you able to share the lower grade more frequent study-related toxicities?

DR. DUGAN: At this time, we are continuing the dose-escalation phase, and it is our intent to present the completed data at a congress venue, scientific congress venue.

DR. JANEWAY: Thank you very much. That's all for me.

DR. PAPPO: Dr. Richard Gorlick?

DR. GORLICK: It's Richard Gorlick. Thank you for the presentation. I have a couple of questions. One, I know in the context of a phase 1 trial it's very hard to ascertain measures of activity, but any comments on measures of activity, particularly for more novel measures, perhaps like your circulating tumor DNA endpoint.

From there, a question about the EWS translocation; did you ascertain the binding partner or was this just one group of rearrangements? Then specifically on preclinical testing -- I'm sorry, I'm covering a lot of ground -- can you talk about combinations with other epigenetic modifiers or other novel agents such as trabectedin or lurbinectedin, just sort of understanding the scope of the preclinical tests.

DR. DUGAN: Yes. Thank you. This is Margaret Dugan, and I'll take the first part of the question. Currently we are at cohorts 6 and 7 of the possible dose-escalation cohorts, and we know from our PK that we are starting to see, that the

exposures are lasting approximately 20 to 24 hours at the dose that we're currently treating at. Given the early nature of the phase 1 study, these data are consistent with phase 1 studies in heavily pretreated patients. We plan to complete the dose escalation and then present the data at a scientific venue.

I think that answers -- oh, in terms of biomarkers, yes, we are doing an extensive biomarker program with circulating pre-DNA CTCs. The tumor tissue comes in at pre-and post-biopsies when we get into dose expansion. We're not quite there yet. We are now starting to look at all of these, so we're assessing the data currently.

I would like to ask Dr. Bruce McCreedy to answer the question about the EWS/FLI.

DR. McCREEDY: Thank you, Margaret.

This is Bruce McCreedy. I'm the acting chief science officer for the company. As you know, LSD1 is critical to Ewing sarcoma cell survival, and a number of studies have demonstrated LSD1 co-localizes and interacts with

transcriptional co-regulators that have been shown to functionally interact with EWS/FLI to modulate enhancer function and reshape gene expression patterns in Ewing sarcoma.

We haven't identified a specific binding partner, but what we do know is that seclidemstat inhibits the ability of LSD1 to efficiently colocalize with some of the same coregulators such as NuRD, which is frequently interacting with EWS/FLI.

We also know that when we study the binding of SP-2577 in Ewing's sarcoma cells and tissue culture, we see decreases in the levels of EWS/FLI protein, which again we assign to the fact that we're inhibiting these co-localizations and that this protein is likely, therefore, being ubiquitinated and pretty similarly degraded with those Ewing sarcoma cell lines.

DR. DUGAN: I think for the third part of your question regarding preclinical testing, you asked about certain specific agents. I'd like to ask. Dr. Aundrietta Duncan to answer that question

for combinations with seclidemstat other than what we discussed earlier for chemotherapy.

DR. DUNCAN: Thank you, Margaret.

This is Aundrietta Duncan again. Thank you, Dr. Gorlick for the question. It's a very good question. As mentioned in the talk, epigenetic factors do not work in isolation, but rather they work in concert with many proteins such that impaired or altered activity with one protein may lead to a functional dependency upon another.

We and others have evaluated a number of indications for additive and synergistic activity of LSD1 inhibition with other epigenetic inhibitors, and there are some preclinical data with HDAC inhibitors and DNMT inhibitors that lead us to believe that this could be a beneficial combination therapy. I have some slides that I could provide more data if you would like. Thank you.

DR. GORLICK: If I'm allowed, I would just ask one clarifying additional question, and that would just be, do you expect this drug to work with

the EWS barium translocations? So a FLI is not the binding partner. Do you expect the same level of activity with this inhibitor?

DR. DUGAN: I'd like to ask Dr. Aundrietta Duncan to answer that question. And before she answers, I can say that we do have an advanced phase 1 study that started after the Ewing sarcoma in which we do allow non-Ewing sarcoma patients on, and we've seen some prolonged treatment durations in patients with desmoplastic small round-cell tumor as well as myxoid liposarcoma. So we do know that they do have the other translocations in EWS/FLI.

I'd like to ask Aundrietta Duncan if there's any preclinical data.

DR. DUNCAN: Yes. This is Aundrietta.

Yes, Dr. Gorlick, we do think that LSD1 inhibition may be efficacious in other EWS fusion-driven diseases. Some of the sarcomas, as Margaret mentioned, that have these family gene rearrangements are the DSRCT with the EWSR1-WT rearrangements and myxoid liposarcoma with the

fused CHOP rearrangement.

There are some published data by third parties with SP-2509, which you may remember from the presentation is a first-generation analog of 2577. We've seen it has demonstrated efficacy in both EWS-ERG fusion containing Ewing sarcoma cell models, both in vitro and in vivo, as well as activity in EWS-WT1 fusion containing DSRCT cell lines. There's also some preliminary data internally that reveals that there may be some activity in EWS/ATF fusion-driven, clear-cell sarcomas.

Does this answer your question?

DR. GORLICK: Yes, that's perfect. Thank you very much.

DR. DUNCAN: You're welcome. Thank you.

DR. PAPPO: I'm going to allow two additional questions. The next person is going to be Dr. Greg Reaman and then Dr. Malcolm Smith, and then we will stop the questions for the sponsor.

Greg?

DR. REAMAN: Thank you, Dr. Pappo.

A couple questions. Can you provide a little bit of clarification on the nonclinical data that led to your dose-escalation paradigm, the starting dose on the escalation, and as I understand, why the 1500-milligram maximum dose?

DR. DUGAN: Yes. Hi, Dr. Reaman. This is Margaret Dugan. The starting dose for the first-in-human studies was based upon the 28-day tox studies in dogs and rats, again, using the standard highest severely toxic dose and using the one-sixth safety margin. The dose escalation followed the accelerated titration design, allowing dose doubling early on, and then with the occurrence of a grade 2 AE slowed down and then went to a 3-plus-3 design.

The 1500-milligram dose was put into the study to begin with, in the protocol, and as earlier stated, the PK, we're highly excited that we do see, although given the short half-life, that we are getting the exposures above 1000 nanograms per mL starting at the 900-milligram dose. We're currently at the 1200 and expect to see 24 hours

continuous exposure.

That level of activity, at 1000 nanogram per mL, should provide submission tumor drug levels, which we saw efficacy in preclinical in vitro and in vivo models. In vitro studies were related to seclidemstat's GR50, which ranged from 400 nanomolar to approximately 1 micromolar across 6 different Ewing sarcoma cell lines.

In addition, in the in vivo studies, we observed tumor growth inhibition when plasma PK levels ranged from 1 micromolar to 3 micromolar in the Ewing xenograft models, so we expect that we will not need to go higher than 1500 milligrams.

DR. REAMAN: Okay. Thank you. Then you mentioned the increased LSD1 expression in sarcomas other than Ewing, notably rhabdo and osteo. Are there any nonclinical data demonstrating antiproliferative effects of seclidemstat in those diseases?

DR. DUGAN: I'd like to ask Dr. Duncan to answer that question, please.

DR. DUNCAN: Thank you, Dr. Dugan.

This is Aundrietta Duncan. Yes, as mentioned, non-Ewing sarcomas do exhibit some of the highest LSD1 expressions across cancer types, so that indicates that there may be a potential dependence on LSD1 for proliferation. We have also run some preclinical experiments in both rhabdomyosarcoma and osteosarcoma with the PPTC. This data shows clear evidence of activity of SP-2577 in both of those to these indications.

DR. REAMAN: Okay. Thank you.

Can I just ask if you have a projection as to what particular scientific venue or when you might be presenting any clinical results from the phase 1 study?

DR. DUGAN: This is Margaret Dugan. We expect that we'll reach the MTD probably by early fall, and then have the dose expansion enrolling very quickly over the next 6 months. So whenever the next cycle of oncology conferences that we can meet, we absolutely will try to get it in as soon as possible.

DR. REAMAN: Thank you.

DR. PAPPO: Malcolm?

DR. SMITH: Thank you, Alberto, and thanks to the Salarius team for the presentation. My question is about the statement in the slide deck that drugs targeting epigenetic reprogramming take time to demonstrate efficacy.

The published results are SP-2509, where there's in vitro testing using 72-hour exposures that demonstrate good concentration response curves, suggesting a more rapid onset of action for SP-2509 or a standard onset of action. Furthermore, for SP-2509, induction of caspase 3 and 7 activity, which would be an early mark of apoptosis, was evident within 15 hours of treatment with SP-2509.

Given this rapid onset of apoptosis, what would be the rationale for expecting delayed responses rather than looking for responses at standard periods after treatment initiation?

DR. DUGAN: Yes. I see your question in two parts. One is referring to the data of SP-2509 from the in vitro study, and the second is the

expectation that epigenetic drugs do take time to elicit efficacy. I'd like to ask Dr. Aundrietta Duncan to answer the first question concerning our data, and then perhaps Dr. Whetstine to answer about the epigenetic time to response in general.

Dr. Aundrietta Duncan?

DR. DUNCAN: Hi. This is Aundrietta Duncan. Could you clarify the question specifically about the data? What is the question about the data specifically?

DR. SMITH: Well, it was related to rather than a delayed onset of activity, for example, like you see with EZH2 inhibition, where responses in vitro may take multiple days, there was induction of caspase within 15 hours. So that's suggesting a fairly rapid onset of action for SP-2509, and that's linked to the idea that responses in the clinic might be expected at standard times after treatment initiation.

DR. DUNCAN: Yes, thank you. I believe that I'm going to pass this question on to Dr. Daniela Santiesteban, who is our director of research

development.

DR. SANTIESTEBAN: Thank you, Aundrietta.

This is Daniela Santiesteban. Yes, you're right. More traditionally, epigenetic agents do take time to show activity. The interesting fact with SP-2577, as Dr. McCreedy mentioned, is that we're not only affecting its enzymatic activities, but also it's scaffolding properties for these proteins or protein interaction. Due to that more robust inhibition of LSD1, we often do see activities sooner than traditionally just strictly enzymatic inhibitors of LSD1.

That's just getting at the unique mechanism and the unique way seclidemstat is inhibiting and targeting LSD1. It's more than just enzymatic activity. It's the scaffolding protein, which has a more pronounced effect on cells.

DR. SMITH: So a more pronounced and more rapid effect is what you're saying.

DR. SANTIESTEBAN: That's correct.

DR. SMITH: Thank you.

DR. McCREEDY: This is Dr. McCreedy. I

might also add that we have seen, and others have seen and published, that different cell lines under different in vitro testing conditions will respond more or less rapidly usually depending upon the degree of dependency on LSD1 demethylase activity versus scaffolding activities.

In fact, we and others have looked at quite a large panel of cell lines and continue to do so. In some cases, we can see responses, as you mentioned, as early as 48 to 72 hours, and in other cases we have to culture cells as long as 7 days. So we also think it depends somewhat on the specifics of the cell lines being tested in vitro in terms of what is the timing to actually measure and get growth inhibition response.

DR. SMITH: Right. But for Ewing sarcoma, can you comment on whether the responses are typically early as in the 2509 data?

DR. McCREEDY: With regard to the Ewing sarcoma cell lines, such as 673, TC71, you're correct. We can usually measure up to a 50 percent growth inhibition within about 72 to 96 hours.

Some of that data has been published and presented for TPTC, and we have some internal data as well.

We also are well aware that when you then take this into in vivo models, some of these cell lines are very responsive and some are less responsive, and that may be the result of timing or it may be the result or the need for a better formulation that gives better exposure in vivo. So it can be difficult to make that leap between in vitro activity and in vivo activity.

DR. SMITH: Thank you.

DR. PAPPO: I see that Drs. Reaman and Smith still have their hands up, so if they can lower them down.

I've been told by Dr. Bonner that we may have a couple of extra minutes because there is only one speaker for the OPH session. So I see that Ira Dunkel and Nita Seibel had their hands up before, and then they put them down. I was wondering if you have any additional questions that have not been answered, Ira and Nita?

Ira, do you want to go first?

DR. DUNKEL: Hi. This is Ira Dunkel, Memorial Sloan Kettering. I had a question about the study design. If I understood correctly, there was a mandatory research biopsy on study, and I'm wondering if this is required for pediatric patients, if this has been acceptable by the IRBs for pediatric patients, and if this is required, whether that may have affected the pediatric accrual and explain why this is largely an adult study. Thank you.

DR. DUGAN: Thank you. This is Margaret Dugan. The pre- and post-treatment tumor biopsies were to begin when we did the disease expansion after we had defined the MTD or recommended phase 2 dose, and the mandatory nature of this was made optional for those less than 18 years of age.

Does this answer your questions?

DR. DUNKEL: Yes.

DR. DUGAN: Okay. Thank you.

DR. DUNKEL: Thank you.

DR. PAPPO: And the final question, Nita?

DR. SEIBEL: Yes. Nita Seibel from the NCI.

I had two questions. First of all, do you know is there any difference in the LSD1 expression in Ewing's patients at the time of diagnosis versus the time of relapse and in patients with localized disease versus metastatic disease?

Then my second question is, in the briefing document, it talked about the focus particularly on relapse or testing once you see activity as a single agent. I was just wondering about the rationale behind that versus if you see activity of the agent as a single agent in Ewing, why wouldn't you consider taking it to the upfront setting such as what COG did with AWS 1221, which was newly diagnosed metastatic Ewing's sarcoma and doing a phase 3 randomized study or even in the localized setting. Thank you.

DR. DUGAN: Yes. Hi. This is Margaret Dugan. We are absolutely planning to understand as a single agent what we currently have with the dose expansion to understand in the relapsed/refractory, needing more than two prior lines of therapy to look at the potential efficacy and safety in that

setting.

For further moving it along into the upfront setting, what you've suggested, I think it will depend on the activity level that we do see. This is something that we wanted to ask, as David Arthur had said in his opening statement, to understand from the committee members what are the possibilities in terms of efficacy endpoints so that we don't miss a signal with our drug in Ewing sarcoma; and what would be some innovative trial designs in order to move the agent forward because we believe that in Ewing sarcoma it is truly an unmet medical need, and there still needs to be some further advances in, as you suggested, the upfront setting.

I'd like to ask. Dr. Damon Reed to comment on the development in moving it into this upfront setting.

DR. REED: Yes. Certainly we hope to identify a signal of activity that would meet everyone's threshold for studying this upfront, and of course that is the long-range goal, is to

improve the care for newly diagnosed patients in Ewing sarcoma.

I do believe that there's also the drug development pathway and trying to identify that signal, which matches a bit more the plan for a relapsed, focused activities signal trial that would follow the phase 1 towards creating that data to show that this agent would have that sort of activity to justify a randomized clinical trial, which would be a high bar, especially for newly diagnosed Ewing sarcoma patients who do quite well.

DR. SEIBEL: Not in the not in the metastatic setting, right?

DR. REED: That definitely is a very good point, Dr. Seibel. I agree that there would be different thresholds of activity or signs of activity that could be used and justified to use it in any of the Ewing sarcoma settings of localized upfront disease, metastatic upfront disease, first relapse or second relapse, and beyond.

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

DR. SEIBEL: Yes. And then I had asked about the LSD1 expression levels, if they knew if there was a difference in the different settings of Ewing sarcoma.

DR. DUGAN: Right. I'd like to ask Dr. Santiesteban to answer that question.

DR. SANTIESTEBAN: Yes. So just to clarify, the question was the LSD1 expression and the metastatic versus localized, and also in the relapsed patients?

DR. SEIBEL: Yes, that's correct.

DR. SANTIESTEBAN: Yes, that's a great question. Right now there's not a lot of data across those different patient types. What we do see in the data is that patient prognosis does correlate with LSD1 expression levels with higher LSD1 expression levels, the patients having poorer patient prognosis. As Margaret mentioned, we will be collecting biopsies during the dose expansion and hope to gain more knowledge around your question.

DR. McCREEDY: This is Bruce McCreedy, if I

may, and we can address this in slide number 6, James. This relates again to the mechanism of action and how inhibition of LSD1 may be active in Ewing sarcoma.

What you're seeing in the slide here is an example of several different inhibitors, including SP-2509, which is our analog of 2577 earlier generation version. What this slide is showing is that you can have very potent inhibition of the enzymatic activity of LSD1, that is its demethylase activity, and yet the cells themselves do not undergo growth arrest.

When we see this with 2509, we believe that this is because the inhibition in the activity that we see -- and this is a 96-hour assay -- has to do with 2509's tower domain interactions. We interact with the tower domain of LSD1, and this prevents a lot of its abilities to interact with other co-regulatory protein complexes that are involved with the EWS/FLI as well as EWS fusion protein.

I'd also like to ask Dr. Whetstine if he would like to comment also on why, then, epigenetic

reprogramming may take more time before we can actually visualize or see in the clinic responses to drugs that work via a mechanism such as 2577.

DR. WHETSTINE: This is Jonathan Whetstine, professor at Fox Chase Cancer Center and a consultant on [indiscernible], as that's an expert area of mine.

Going to the question that was asked in regards to what Bruce just said, the time it takes, it is twofold. One is if there's immediate oncogenic dependency, you might see a robust effect. At the same time, to reprogram the epigenome, it can take time based on cell division. So there are two levels that that can be at play, and for several other epigenetic drugs that are out there, that has been observed.

So you can have an immediate response, but then also one has to take into account division time and potentially the capacity and how that will allow the epigenome or the structure around the DNA of cells change. Thanks.

DR. PAPPO: Thank you.

Nita, does that answer all your questions?

DR. SEIBEL: Yes, thank you, Alberto.

Open Public Hearing

DR. PAPPO: Okay. If you still have your hand raised, please lower it. We're going to move on to the next portion of the meeting. Thank you very much for the presenters and thank you very much for asking these questions to the sponsor.

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

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have related to the topics of this meeting. Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do

not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

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

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you're representing for the record.

DR. ZELDES: Good morning, and thank you for

the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Nina Zeldes, a senior fellow at the center. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

We strongly support the FDA and committee's goals to suggest recommendations for clinical trials of treatments for pediatric cancers during these meetings taking place over the next two days. Where aggressive childhood cancers are often fatal, it is essential to carefully study benefits and risks to determine if the likely benefits of a specific indication outweigh the risks.

My statement today is relevant to all the drugs you're considering today and tomorrow. When evaluating drugs for pediatric use, doses must be scrutinized cautiously for children of different ages and weights. Even when there are likely benefits for children on average, it is important

to minimize risks whenever possible by determining which children are most and least likely to benefit. It is also important to consider whether patient demographics affect the benefit and risk.

With this in mind, we strongly urge you to recommend that all clinical trials should include subgroup analyses for sex, race, and age. We understand that this is difficult in rare diseases, but at least some demographic differences are likely to increase or reduce the risks or benefits.

Risk-benefit profiles should, when possible, be assessed for each particular subgroup. For example, with the known very serious adverse events of MRZ, to be discussed later today, it is important to determine which types of patients in terms of demographics are most likely to benefit, and in addition to targeting patients most likely to benefit, are there other ways to mitigate risks.

One of the discussion questions for MRZ addresses mitigating risks for pediatric patients. We suggest that risk mitigation be considered for all four drugs that will be discussed over the

course of these next two days. We understand the desire to get new treatments to patients who desperately need them as quickly as possible, but it is important to make sure the clinical trials are appropriately designed to clearly answer questions of safety and efficacy.

Poorly designed trials, trials with too few patients or too few patients representing key demographic groups, or with poorly selected endpoints do not provide clinicians and patients the information that they need to make informed decisions. Parents want to have hope for their children, but no parent wants to subject their child to treatments with horrible side effects unless those treatments can eventually significantly improve how long they live or their quality of life.

Efforts to design the best possible clinical trials and to protect patients who participate in those trials, or who may eventually be prescribed cancer drugs, are essential. Even if clinical trials take a little longer but are more

informative and conclusive, they will in the long run help more patients and harm fewer patients, which is everyone's goal. Thank you.

Questions to Subcommittee and Discussion

DR. PAPPO: Thank you very much.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the public. The subcommittee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. We will now proceed with the charge and questions to the subcommittee and panel discussions. After each question is read, we will pause for any questions or comments concerning its wording, then we will open the questions for discussion.

DR. DOROS: Good morning. This is Leslie Doris, FDA. Thank you, Salarius for a very informative presentation.

For the pediatric ODAC panel members, we have three discussion points today. Our first discussion point is given that SP-2577 targets LSD1

and studies have demonstrated increased expression of LSD1 and other tumor types, in addition to Ewing sarcoma, please address other pediatric solid tumors and hematologic malignancies in which there is a biologic rationale for evaluation of its activity.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the question to the discussion. I think I was the first one to raise a hand, so I'll go first if you don't mind.

I think that, personally, the data that was presented on other tumors was a little bit weak. The sponsor also mentioned that there was some evidence of activity in the preclinical testing program, but if you look at the briefing document, they had 5 alveolar rhabdomyosarcoma models and 6 osteosarcoma models, and all they saw were prolongation to event. There were no responses or objective responses in any of their models.

I think that the data was a little bit scanned. Also, I don't know how LSD1

overexpression really correlates with response or clinical activity with the lack of any functional studies, so that was just one of my observations.

Will the next person please introduce yourself, Dr. MacDonald?

DR. MacDONALD: Hi. This is Toby MacDonald from Emory. In terms of solid tumors related to CNS, several recent publications indicate LSD1 is a potential therapeutic target in a variety of pediatric brain tumor types. These include medulloblastoma, DIPG, pediatric high-grade glioma, and ATRT. In some histologies especially, there appears to be an immune sensitizing effect and also efficacy in combination with HDAC inhibitors preclinically.

So the questions that I would like back to the company would be whether this agent crosses the blood-brain barrier; and if so, if there are any in vitro or in vivo data for pediatric CNS tumor models or consideration testing in these models in the future, particularly the HDAC inhibitors or, say, checkpoint inhibitors. That's all.

DR. DUGAN: Yes. Hi. This is Margaret Dugan. In terms of crossing the blood-brain barrier, in tissue biodistribution studies in healthy non-CNS, tumor-bearing animals, the fraction of SP-2577 found in brain versus plasma is about 3 percent. I'd like to also now refer to Dr. Aundrietta Duncan with regard to other preclinical studies in terms of CNS tumors or in combination, as you've asked.

DR. DUNCAN: Thank you, Margaret.

This is Aundrietta Duncan. Yes, there definitely have been some recent studies showing that combinatorial treatment of DIPG with LSD1 inhibitors as well as HDAC inhibitors do demonstrate energy. There are a couple of published studies. One is not with our molecule. There's one that is with our molecule, so those studies are encouraging, and some of those studies are ongoing.

I believe there was a second part to your question. Could you remind me of the second part of your question?

DR. MacDONALD: The question was just whether you have any in vitro or in vivo data for your particular agent with regard to pediatric CNS tumor models and/or consideration of testing in such models.

DR. DUNCAN: Yes, sure. As I mentioned, those data are available and some of those studies are ongoing.

DR. DUGAN: Thank you.

DR. McCREEDY: This is Bruce McCreedy. I believe you might have also asked the question about immune sensitization and the potential for combination with checkpoint inhibitors for instance; is that correct?

DR. MacDONALD: Yes. Thank you.

DR. McCREEDY: Yes. In fact, we have studied this, and we do have some data and some publications recently with our compound that indicates that among the activities that LSD1 is involved in, that inhibition can help, is interactions with the risk complex. Specifically, LSD1 seems to affect the risk complex and increases

the amount of cytoplasmic double-stranded RNA mostly from endogenous retroviral sequences. What that does is it can kick off the cells' double-stranded RNA sensors, leading to a type 1 interferon response.

We did look at this. We looked at it in a variety of tumor types, including some that have specific mutations in chromatin remodeling complexes such as within the SNP pathway. And we did in fact show that when we inhibit the LSD1 activity with our compound, we do see increased immunogenicity of these tumors as evidenced by infiltration of those tumors by cytotoxic T cells, primarily CD8 T-cells.

We then went on to study this in a couple of models as well as others, one being in a syngeneic breast tumor model where clearly a combination of our drug with an anti-PD-1 inhibitor led to more significant tumor growth. In addition to that model, we also looked at this through a collaborator in the syngeneic colon tumor, the CT26 model, and showed that there was also enhanced

activity with anti-CTLA-4 inhibitors.

So there is a rationale and there is evidence that inhibiting LSD1 activity can in fact help make tumors more immunogenic via the production of type 1 interferon response and recruitment of other players within the innate pathways of immune response, as well as via causing those cells to upregulate more of their MHC 1 expression and therefore be more immunogenic.

DR. MacDONALD: Thank you.

DR. PAPPO: Dr. Glade Bender? Julia?

DR. GLADE BENDER: Thank you. Julia Glade Bender. With regard to this question about SP-2577 in tumors additional to Ewing sarcoma, I find myself a bit confused about what is the potential biomarker to identify potentially sensitive tumors. Is it the increased expression of LSD1 or is it the translocation type? I wonder if additional preclinical studies using panels of TDX or otherwise might help us to discern what is the most powerful biomarker that could be used for patient selection of those most likely to respond.

DR. DUGAN: Yes. Hi. This is Margaret Dugan. I think in terms of the biomarkers we are exploring in the clinic, we are looking at circulating tumor cells for gene expression profiles during the dose escalation to look for any expression patterns that could solidify exactly the inhibition of LSD1 by our agent.

I think more importantly, and we're close to this when we get to the disease expansion, we will be able to have those pre- and post-tumor biopsies and be able to explore to a better extent those changes in gene expression profiles, demonstrating that we are hitting the target and effectively translating that into tumor responses.

The other part of your question? I'm sorry.

DR. GLADE BENDER: No. I guess it's just a general comment. When I look at the LSD1 expression, for example in rhabdomyosarcoma and it's not clear to me whether those were alveolar or embryonal models, there is the level of expression of LSD1, but that may or may not communicate how dependent they tumor is on LSD1 in terms of what is

driving its growth. And the question is really whether that is determined by a translocation or whether LSD1 expression in and of itself, a high level of it, is actually a predictable response.

DR. DUGAN: Right. We will, during this extensive biomarker, be looking at the different EWSR1 translocation patterns and also essentially by IHC measure LSD1 protein level expression.

DR. PAPPO: Okay. The next question is from Dr. Malcolm Smith.

DR. SMITH: Yes. This is Malcolm Smith. The first point I wanted to make was with increased protein expression in the absence of the genomic alteration, this is not predictive of clinical benefit for targeted agents in most settings. In the absence of functional genomic studies, it's hard to know what role LSD1 inhibition and/or not found might have in terms of therapeutic potential for other pediatric solid tumors. I would endorse Alberto Pappos' comment about the PPTC data as well.

A specific comment about the immune

checkpoint inhibitors is that Ewing sarcoma, as one example, is an immunologically cold tumor for which there's really no evidence of response to checkpoint inhibitors and really little or no evidence for the immune system being able to recognize these tumors as foreign.

So before getting into combinations with an agent like SP-2577 in a cold tumor like Ewing sarcoma, I think it would be really important to see preclinical models of immunologically cold tumors with low tumor mutational burden and/or the ability of an agent like SP-2577 to convert an adult immunologically cold tumor with low tumor mutational burden into a checkpoint responsive tumor.

DR. PAPPO: Thank you, Malcolm.

The next question is from Dr. Gorlick.

DR. GORLICK: It's Richard Gorlick. I find some of the most compelling preclinical data, the evidence around the reversal of the transcriptional signal driven by EWS/FLI. I am somewhat intrigued about the idea of the spectrum of translocations

associated with EWS that may show activity in response to this. I think that can be probed in the context of clinical trials by getting the break-apart fusion, so you know whether it's specifically EWS/FLI or a different binding partner.

The other areas that you could think about exploring are desmoplastic small round-cell tumor, which has already come up earlier. There's not a lot of preclinical models, but a couple do exist, and obviously it's a clinical entity as well. I also wouldn't forget the adult sarcomas, so clear-cell sarcoma also has EWS fusion, and I wonder whether you have data thus far, or planning to obtain data, to explore the spectrum of EWS related activity. Thank you.

DR. DUGAN: Margaret Dugan. I guess, Dr. Gorlick, you're asking Salarius to answer this, correct?

DR. GORLICK: Yes. I'm questioning whether you have any data on clear-cell sarcoma and desmoplastic small round-cell tumor beyond what's

already been mentioned or plans to look at those.

DR. DUGAN: Right. Thank you. You refer back to my statements about in the clinic how we've advantageously been able to enroll some of these patients. I'd like to ask. Dr. Aundrietta Duncan to answer that about the preclinical activity that we may not have ongoing.

DR. DUNCAN: Thank you, Dr. Dugan.

This is Aundrietta. Dr. Gorlick, to answer your question, the data that we mentioned, that one publication with DSRCT with 2509 and then the really early preclinical NDO study that we have in clear-cell sarcoma with the EWS-ATF1 fusion, those are the extent of the data that we have at the moment, but certainly I do agree with you that understanding the biology with different fusions is certainly warranted and something that we could consider doing.

DR. GORLICK: Thank you.

DR. DUNCAN: Yes. Thank you.

DR. McCREEDY: This is Dr. McCreedy. I'd like to also respond to your question that we are

in fact evaluating over 160 different cell lines in a very extensive study right now where we will be asking some of the very questions you are, including looking for and correlating specific mutations in various chromatin remodeling complexes. We have identified some that we know do sensitize more to our inhibitor such as the SMAR-K4 [ph] and ARID1 that are part of the SWI/SNF pathway.

We are also continuing with our accommodations for immuno-oncology in that we are questioned about a cold tumor such as Ewing's tumor and making it hot. We have looked at the tumors, including cold 434, which is normally an immunologically cold tumor and have noted that we do turn that into, quote/unquote, "a hot tumor" that we can demonstrate clear-cut infiltration now by mononuclear cells, by T cells, into those tumors after incubation with the compound. We've also seen an MCF-7 line.

So I think your comments are right on target, and rest assured we are very thoroughly

evaluating all of these different questions to try and ascertain better different potential combination mechanisms, as well as what are the specific targets, as you saw from the RNA-Seq profile, can we identify specific other targets, which we believe are more likely in the case of Ewing's not to be the EWS/FLI protein itself but rather one of its many interacting corepressor/coactivator complexes. One of the proteins within those complexes is more likely to target.

DR. PAPPO: Okay. Dr. Cheng. And I would like to remind the panel that the purpose of this session is really to have discussion amongst panel members, so we will have Dr. Cheng ask a question.

DR. CHENG: Sure. Thank you, Dr. Pappo.

I actually had a question regarding the context of this question of other tumors. My question is actually to the FDA, if they can give guidance as to how they think about how a compound should be investigated in other tumors, the extent of the investigation, and should it be limited

based on the science knowing that this is difficult to investigate every single tumor, particularly in the context of a written question.

I do think that will be helpful, to have an understanding as to how the FDA is viewing the opportunities or the limitations investigating other tumors and how extensive or limited it should be.

DR. PAPPO: I don't know if Greg wants to answer that or another member of the FDA.

DR. REAMAN: This is Greg Reaman. I can try to answer Dr. Cheng's question. Part of the reason for this question was because of the fact that our policy, if you will, in issuing written request, is to make sure as best we can that the investigational drug that's being explored addresses as many or all of the potential public health considerations in the pediatric age group.

When we consider issuing written requests, we want to make sure that we are addressing all of the possible indications that might be addressed by a particular drug in children. In saying that,

we're not requiring that sponsors necessarily do exhaustive investigation of every single pediatric cancer in that situation, but the question here was raised because of the lack of clarity regarding LSD1 expression versus the existence of one or more specific fusions related to the various partners that were associated with the proliferative activity in the growth of Ewing's, and then also with the activity of SP-2577.

So that was the basis for the question. I've answered it for you.

DR. CHENG: Thank you, Dr. Reaman. I forgot to identify myself. This is Jon Cheng, industry rep, and I do appreciate a practical approach. Particularly sometimes small companies or even big companies wish to be focused in their investigation of other tumors, and sometimes preclinical or early clinical data is sometimes thought to be maybe adequate as to how to investigate this, but thank you for that helpful response.

DR. REAMAN: Sure.

DR. PAPPO: If Dr. McCreedy could please lower is hand.

If there are no additional questions, I will try to summarize what we discussed for question number 1. The first one was that it is unclear whether increased protein expression of LSD1 will predict any kind of response, and additional studies, including functional genomics, are highly encouraged.

In addition to that, the preclinical data that was presented for other tumor types seemed, in my opinion, a little bit weak, especially for alveolar rhabdomyosarcoma and osteosarcoma, so perhaps additional studies need to be conducted. There also was talk about combination therapy with LSD1, however, we were unable to see that data. So it would be important to see if there's really a synergistic effect by adding other chemotherapeutic agents or other therapies to LSD1 inhibitors.

There was an issue about considering brain tumors for this specific drug. If I understood correctly, the blood-barrier penetration is

relatively low. I think it was 3 percent. So I am not sure that additional studies in brain tumors should be conducted or not, but I'll ask our CNS experts to chime into that portion of the summary.

There was also a suggestion to further explore potential biomarkers that will allow a better prediction of response in these patients. There was also a suggestion that if combination with immunotherapies is to be conducted that additional preclinical studies are done since Ewing sarcoma specifically appears to be a cold tumor. There was also a question about increasing the spectrum of when to use this therapy in other EWS rearranged tumors, desmoplastic small round-cell tumor and clear-cell sarcoma.

Finally, Dr. Reaman explained the FDA's view when considering a written request and to explore all the possible indications of a particular drug.

Could you raise your hands or say if I missed anything? Specifically, Tobey, did I address the CNS issue correctly or did I miss something?

DR. MacDONALD: This is Tobey. No, I think you addressed it correctly. The question would be whether 3 percent, the activity of the drug is viable as a mechanism at that level. We know that other chemotherapies such as cisplatin has a very low percentage across the blood-brain barrier by 2 to 4 percent, so it really comes down to activity of the drug at that level.

DR. PAPPO: Thank you very much. If I didn't mess up very badly or if I didn't miss anything, we're going to move to the next question. The FDA would read the second question to the committee.

DR. DOROS: I'm just waiting for the slide to change.

Question 2. Thank you. For discussion point number 2, given the nonclinical results of synergistic effect in increased antitumor activity of SP-2577 in combination with chemotherapeutic and epigenetic agents and immune checkpoint inhibitors, consider its use as a combination treatment in pediatric tumors.

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

DR. JANEWAY: I'm sorry. That was to raise my hand for discussion.

DR. PAPPO: Anyone else want to ask -- I think some of these points were discussed in question number 1. I think Dr. Greg Reaman has his hand raised.

DR. REAMAN: Yes. I was just going to say the same thing, Alberto. I think we actually covered many of these points in our discussion of the previous question.

DR. PAPPO: Let me just keep going down the list and see if there's anything else that we are missing.

Malcolm? Malcolm, do you have a question?

DR. SMITH: Alberto, are we having discussion now on this point or questions about this point?

DR. PAPPO: No, we're having discussion

about this point.

DR. SMITH: Okay. So Katie will join in as well, then. The point I would make here is that the best predictor for success in combination regimens is activity as a single agent. Not every single agent with activity will improve outcome when it's used in combination, but agents without single-agent activity have a much lower likelihood of improving outcome when used in combination.

To illustrate this, we did a retrospective study looking at CTEP-sponsored randomized phase 2 trials in which an experimental agent was added to a known active agent, and fewer than 3 percent of these randomized trials that involved experimental agents without documented single-agent activity for the disease under evaluation produced results that were indicative of likely true clinical benefit.

So I think the appropriate step now would be to look for the single-agent activity against Ewing sarcoma like Salarius is doing, and we're certainly all hoping that there's going to be good, robust activity observed, and at that point it's a

no-brainer to proceed to combination studies.

If there's not single-agent activity, then I think we'll have to think long and hard about what the next steps are for Ewing sarcoma or other EWS rearranged tumors, and that would have to be done, in part, based on what preclinical data existed but also in the context of other research opportunities for patients with Ewing sarcoma. Thank you.

DR. PAPPO: Thank you very much.

Katie still has her hand raised. Do you want to have a little bit of discussion on this question?

DR. JANEWAY: Yes. I wanted to comment on this question, so thank you for asking this question. I think it's a very important question, which is why it came up in the discussion of the first question.

I do think that if there is evidence of single-agent activity, particularly if the toxicity signal remains reassuring, that there will need to be consideration of combination studies with chemotherapy.

If you are thinking about more long term in terms of which setting would you imagine that this drug would be used in Ewing sarcoma, most likely you would want to study this in the newly diagnosed setting, and in that setting you would likely be combining it with some type of Ewing sarcoma drug to chemotherapy. Even if you were to set your ultimate goal on use of this, for example in first recurrence, it's very likely that you would want to combine those with one of the chemotherapy regimens that is used at the time of relapse in Ewing sarcoma.

So I would encourage the company and the other investigators who are working with this compound to continue to study in the preclinical space activity in combination with chemotherapy agents that are used in Ewing sarcoma.

I do also think that it would be very interesting to better understand the mechanism by which there might be synergy with immune checkpoint inhibitors as was already discussed in terms of converting what is thought to be a cold tumor into

a more hot tumor in the setting of combination with immune checkpoint inhibitors. Thank you very much.

DR. PAPPO: Thank you, Katie.

Leo, you're next.

DR. MASCARENHAS: Hi. This is Leo Mascarenhas. Can you hear me?

DR. PAPPO: Yes, we can.

DR. MASCARENHAS: This question is an intriguing one, and when you look at pediatrics sarcomas in particular, they're rapidly proliferating in aggressive cancers, and oftentimes the time to progression, especially at the time of relapse, is relatively low.

I struggle with if there is a lot of robust preclinical activity, and testing of a drug in a phase 1 setting to make decisions based on just purely clinical activity in that setting may be challenging. I think the example which we all know was I think with temsirolimus and rhabdomyosarcoma and mTOR inhibition, where a single-agent therapy didn't show any exciting clinical activity, but the preclinical information was very strong and the

combinatorial therapy in preclinical models was also excellent. We were able to show at least some activity in the relapsed setting, and it is now being tested in the upfront setting.

So while single-agent activity would be very encouraging and would help us to move this rapidly forward, if there is robust preclinical activity, I'm not sure whether we absolutely need clinical activity in the phase 1 setting to think of a possibility of moving a very active agent preclinically forward, though it will be helpful. Clinical activity will be helpful, but I don't know if it should be the sole decision.

DR. PAPPO: Even in the presence of the fact that all of the patients that are being tested with those drugs are patients with Ewing sarcoma, if you didn't see any responses in I think 16 or 17 patients, despite the fact that you have robust preclinical activity, you would still consider moving this forward with combination therapy?

DR. MASCARENHAS: If the preclinical combination data, which can be generated, is robust

particularly in Ewing sarcoma and we have a hint of clinical activity in terms of some disease stabilization rather than responses, given the landscape of potential active agents in Ewing sarcoma, I might consider at least a trial in the relapsed setting.

DR. PAPPO: Thank you very much.

I see Katie still has her hand up. Do you still want to comment on this question or you're okay, Katie?

DR. JANEWAY: My apology. I'll lower my hand.

DR. PAPPO: If there are no additional comments on this question, if I could briefly summarize this. A lot of the issues raised in this question were already addressed in question number 1, however, one point of view would be to look for single-agent activity in this clinical trial, and if there is no robust single-agent activity, it would be difficult to justify combination studies.

On the other hand, there is a precedent for

preclinical studies that have shown activity of some single agents, for example temsirolimus, and lacked significant clinical activity as a single agent. However, when they were combined with chemotherapy in the preclinical models, they appeared to be a synergy, and actually in the clinical setting, they proved to be efficacious in the setting of relapsed rhabdomyosarcoma.

So one point of view would be if there is no single-agent activity, try to pursue combination studies. The other point of view from the panel is if there is very strong preclinical activity with combination therapies to at least pursue a phase 1 clinical study in the relapsed setting of Ewing sarcoma.

Did I capture the conversation okay, or did I miss anything, or did I mess up anything, Leo or Malcolm?

DR. SMITH: That was clear, Alberto, from my perspective. This is Malcolm Smith.

DR. PAPPO: Thank you very much.

DR. MASCARENHAS: It's clear from my

perspective, too.

DR. PAPPO: Thank you very much. We will now proceed to the third question. The FDA will read the third question.

DR. DOROS: Hi. For our last discussion question today, please discuss the use of SP-2577 in patients less than 12 years of age given the range of tumor types that appear to be susceptible to the antitumor effects of SP-2577 based on nonclinical data.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the question for discussion. I see Leo has his hand up.

Leo?

DR. MASCARENHAS: As a pediatrician, I would support investigating this in patients less than 12 years of age, at least in select cancers. The median age of Ewing sarcoma is in the teenage years, and we do have several patients who are below the age of 12 who could potentially benefit.

DR. PAPPO: Thank you very much. I also see

a bunch of hands. The next one is Dr. Gorlick.

DR. GORLICK: It's Richard Gorlick. I'm actually going to recommend the other way. Ewing sarcoma, even though there are patients who are below 12, the vast majority are above it. Clear-cell sarcoma is an adult condition, and desmoplastic small round-cell tumor is an adolescent and above disease.

Most of the entities you're talking about are going to be easily feasible for an activity study to be done in an over-12 group; and although you ultimately, if there is activity, may want to know the safety in younger patients, you're going to be able to get an activity assessment in the older age range, and I'm not sure there's enough histology to justify needing to do a peds 12-and-below study right away. Thank you.

DR. PAPPO: Elizabeth?

DR. RAETZ: Hi. This is Elizabeth Raetz. I think one thing is if it were to be considered in the less-than-12 year olds, it would be to have a better understanding of plans for alternate

formulations. It may be hard in a pill form that's a small pill, so it's a fair number of pills to take with each dose. So it might be helpful to understand if other formulations are planned.

DR. PAPPO: Thank you. Katie?

DR. JANEWAY: Yes. I was going to say something similar to what Richard Gorlick said. I think that you can wait to expand to understand dosing and tolerability in patients under 12 years old with Ewing sarcoma until you have signals from your dose in terms of whether or not there is evidence of clinical activity.

DR. PAPPO: Thank you. And just a brief reminder to please introduce yourself when you're commenting on the question, and then go ahead. I see that hands are still raised for Elizabeth, for Katie, and for Leo. Unless you have another question, please lower your hand.

Let me see where we're at here. I have Leo still.

DR. MASCARENHAS: Can you hear me?

DR. PAPPO: Yes, we can hear you. Go ahead.

DR. MASCARENHAS: This is Leo Mascarenhas. I was on mute. For testing in children younger than 12 years of age can take a while, and waiting for activity in Ewing sarcoma may hamper further development in pediatrics, particularly if preclinical data could be used to generate information to test this in patients with rhabdomyosarcoma, where the majority of patients are less than 12 years of age. So considering it broadly, issues related to pharmacokinetics, safety, as well as formulation is important in my opinion. Thank you.

DR. PAPPO: Thank you very much. Ted is the next one.

DR. LAETSCH: Hi. It's Ted Laetsch. I was just going to second what the other advisory committee members had said, that while we certainly can look at activity in patients over 12, it will take some time to think about a pediatric formulation if one is necessary or at least smaller dosing increments like your current dosing increment that would enable a pediatric study. I

would encourage us to think about those issues earlier rather than later so that it isn't only after there's evidence of activity in adults if those begin to be considered.

DR. PAPPO: Thank you, Ted.

Dr. Cheng?

(No response.)

DR. PAPPO: Ira?

DR. DUNKEL: Ira Dunkel, Memorial Sloan Kettering. I wanted to ask fellow committee members who are more sarcoma oriented than I am if we should be surprised that there have been so few adolescents who've been enrolled on the existing trial. I realize that's a little tangential to this question but might impact on even younger patients choosing to access a drug. Thank you.

DR. PAPPO: I think part of it would depend on the number of centers that had this clinical trial open and the type of patients they're seeing and if they're mostly adults centers. I don't have that clinical trial open here, so I will ask some of the panel members that have their clinical trial

open at their institution if it's an issue of older age of the patients with relapsed Ewing's or the fact that they're mostly seen by your adult counterparts?

I think I see Katie's hand, so Katie, go ahead.

DR. JANEWAY: I would say it's a combination of both of the factors. Sorry. Katie Janeway, pediatric oncology, Dana-Farber. I would say it's a combination of both of the factors. You mentioned, Alberto, one is the site where the trial is open and the other is actually the age of our relapsed Ewing sarcoma patient population who tend to be older.

So even when we run a trial like this through the Children's Oncology Group, which is exclusively pediatric centers, we see a good quarter of the patients being over age 18.

DR. PAPPO: Ted has a comment also.

DR. LAETSCH: Apology. I just didn't put my hand down.

DR. PAPPO: Are there any additional

comments about this question? Leo has one. Yes?

DR. MASCARENHAS: I was just going to add that the outcomes relatively of Ewing sarcoma have improved in recent years, and younger patients tend to have a better prognosis. The other requirements are that oftentimes there are other therapies which are usually considered at first relapse, so many of the patients, as you could see from the data which was presented, were beyond first relapse, and that may contribute also to the older age of the patient.

DR. PAPPO: Thank you, Leo.

If I could summarize the discussion on this third question, most of the panel members that commented on this question feel that we should have more data on patients over 12 years of age because the vast majority of patients that present with Ewing sarcoma will be in this age group. However, some panel members think that specifically for other histologies other than Ewing's, for example, rhabdomyosarcoma, there are clinical trials that are going to be conducted in these specific

histologies, and that less than 12 years of age should be taken into consideration for enrollment to the clinical trial. In addition to that, that would give us the opportunity to better assess the PK of this compound in this population and also investigate alternative formulations.

Regarding the rate of enrollment of younger patients in the current ongoing trial, the reason why there are such few patients might be related to the fact that the number of institutions that have this clinical trial open, the age of patients with Ewing sarcoma, the time of relapse, and the fact that some of these patients have improved outcomes and go on other therapies prior to going to experimental therapies; for example, the rEECur trial is the perfect example, irinotecan, temozolomide, ifosfamide, and cyclo [indiscernible].

I think I've summarized the discussion of question number 3. Unless there's anything I've missed, I welcome your comments or suggestions.

(No response.)

Adjournment

DR. PAPPO: Okay. If there are no additional comments, we will now break for lunch. We will reconvene at 1:20 p.m. Eastern Standard time. Panel members, please remember that there should be no discussion of the meeting topics during lunch amongst yourselves or with any member of the audience. Thank you very much, and we will see you back in a little bit. Thank you very much.

(Whereupon, at 12:05 p.m., the morning session was adjourned.)