FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE PEDIATRIC SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE (pedsODAC)

Morning Session

Tuesday, June 28, 2016

8:00 a.m. to 11:08 a.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Lauren D. Tesh, PharmD, BCPS
Division of Advisory Committee and
Consultant Management
Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Deborah K. Armstrong, MD
Professor of Oncology
The Sidney Kimmel Comprehensive Cancer Center at
Johns Hopkins
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Alberto S. Pappo, MD
(Chairperson, pedsODAC)
Member and Head, Division of Solid Malignancies
St Jude Children's Research Hospital
Professor of Pediatrics
University of Tennessee Health Science Center
Memphis, Tennessee

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Non-Voting)

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

(Industry Representative)

Executive Medical Director, Amgen Oncology

Therapeutic Area Head, US Medical Organization

Thousand Oaks, California

TEMPORARY MEMBERS (Voting)

Peter C. Adamson, MD

(Day 1 Only)

Chair, Children's Oncology Group

Alan R. Cohen Endowed Chair in Pediatrics

The Children's Hospital of Philadelphia

Philadelphia, Pennsylvania

Patrick Brown, MD

Director, Pediatric Leukemia Program

Associate Professor of Oncology and Pediatrics

Sidney Kimmel Comprehensive Cancer Center

Johns Hopkins University School of Medicine

Baltimore, Maryland

Steven G. DuBois, MD, MS
Director, Experimental Therapeutics
Dana-Farber/Boston Children's Hospital
Faculty of Pediatrics, Harvard Medical School
Boston, Massachusetts

Ira J. Dunkel, MD
Member Memorial Sloan-Kettering Cancer Center
Professor of Pediatrics
Weill Cornell Medical College Department of Pediatrics
New York, New York

Julia Glade Bender, MD
Associate Professor of Pediatrics at Columbia University Medical Center
Associate Director, Division of Pediatric Hematology, Oncology and Stem Cell Transplantation
Medical Director, Developmental Therapeutics and Precision Medicine Programs
New York, New York

Pamela Haylock

(Acting Consumer Representative)

Medina, Texas

Tobey J. MacDonald, MD

Aflac Chair for Pediatric Neuro-Oncology

Professor of Pediatrics

Emory University School of Medicine

Director, Pediatric Neuro-Oncology Program

Aflac Cancer & Blood Disorders Center

Children's Healthcare of Atlanta

Atlanta, Georgia

Gigi McMillan

(Patient Representative)

Manhattan Beach, California

Kathleen A. Neville, MD, MS

Director, Experimental Therapeutics Program

Professor of Pediatrics, University of Arkansas for Medical Sciences

Section of Clinical Pharmacology and Toxicology

Arkansas Children's Hospital

Little Rock, Arkansas

Elizabeth A. Raetz, MD

Professor of Pediatrics

Pediatric Hematology/Oncology

University of Utah

Huntsman Cancer Institute

Primary Children's Hospital

Salt Lake City, Utah

Nita L. Seibel, MD

Head, Pediatric Solid Tumor Therapeutics

Clinical Investigations Branch, CTEP/Division of

Cancer Treatment and Diagnosis

National Cancer Institute, NIH

Adjunct Professor of Pediatrics

George Washington University

School of Medicine and Health Sciences

Bethesda, Maryland

Katherine E. Warren, MD

Head, Pediatric Neuro-Oncology

Pediatric Oncology Branch

National Cancer Institute, NIH

Bethesda, Maryland

Brenda Weigel, MD, MSc

Associate Professor

Developmental Therapeutics Chair

Children's Oncology Group

Division Director, Pediatric Hematology/Oncology

University of Minnesota

Minneapolis, Minnesota

FDA PARTICIPANTS (Non-Voting)

Richard Pazdur, MD

Director

Office of Hematology Oncology Products (OHOP)

Office of New Drugs (OND), CDER, FDA

Gregory Reaman, MD

Associate Director for Oncology Sciences

OHOP, OND, CDER, FDA

Amy Barone, MD

(Morning Session, Day 1)

Medical Officer

DOP II, OHOP, OND, CDER, FDA

Lori Ehrlich, MD, PhD

(Morning Session, Day 1 Only)

Medical Officer

DHP, OHOP, OND, CDER, FDA

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

(8:00 a.m.)

Call to Order

Introduction of Subcommittee

DR. PAPPO: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices, if you have not already done so.

I would also like to identify the FDA press contact, Angela Stark. If you are present, please stand.

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

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

DR. BROWN: Pat Brown, pediatric oncologist, Johns Hopkins.

DR. WARREN: Kathy Warren, pediatric neuro-oncology, National Cancer Institute.

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

DR. DUNKEL: Ira Dunkel, pediatric oncology, Memorial Sloan Kettering.

DR. DuBOIS: Steve DuBois, pediatric oncology, Dana-Farber/Boston Children's.

MS. McMILLAN: Gigi McMillan, patient liaison.

MS. HAYLOCK: Pamela Haylock, the acting consumer representative.

DR. ARMSTRONG: Deborah Armstrong, medical oncologist and chair of adult ODAC.

DR. PAPPO: Alberto Pappo, pediatric oncology. I'm the chair.

DR. TESH: Lauren Tesh, DFO.

DR. NEVILLE: Kathleen Neville, pediatric oncology and clinical pharmacology.

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

DR. MacDONALD: Tobey MacDonald, pediatric oncology, Emory University.

DR. GLADE BENDER: Julia Glade Bender, pediatric oncology, Columbia University.

DR. SEIBEL: Nita Seibel, pediatric

oncologist, National Cancer Institute.

DR. ADAMSON: Peter Adamson, pediatric oncology, clinical pharmacology, Children's Hospital of Philadelphia.

DR. EHRLICH: Lori Ehrlich, pediatric oncology at the FDA.

DR. BARONE: Amy Barone, pediatric oncology, FDA.

DR. REAMAN: Gregory Reaman, FDA.

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

FDA Introductory Remarks/Presentation

DR. REAMAN: Thanks, Mr. Chairman. I'd like to just thank all of the participants here for coming. I know this is difficult, particularly during this time of the year, but we really do very much appreciate your participating in this subcommittee meeting and providing consultation and advice to the agency about the potential pediatric development of some novel agents.

As you know from the background material that you received, there are two pieces of

legislation which heavily impact pediatric drug development, Pediatric Research Equity Act, or PREA, and the Best Pharmaceuticals for Children Act, or BPCA.

PREA has very little relevance to pediatric cancer drug development because the mandate for pediatric assessments and evaluations is driven by the fact that the medication or drug product in question has to be used for the same indication. Cancers of adults and children are obviously very different, and I don't have to tell you that.

We are attempting to maximally utilize the authority provided to us by or through the BPCA. The Best Pharmaceuticals for Children Act expressly charged this pediatric subcommittee in carrying out its mission to review and evaluate data concerning the safety and effectiveness of marketed, as well as investigational human drug products for use in the treatment of pediatric cancers.

To do so, it shall evaluate and, to the extent practicable, prioritize new and emerging therapeutic alternatives available to treat

pediatric cancer, provide recommendations and guidance to help ensure that children with cancer have timely access to the most promising new cancer therapies, and advise on ways to improve consistency in the availability of new therapeutic agents.

We're here for this meeting to discuss five new products in varying stages of development, some still investigational, some approved, some are actually in the phase 1 evaluation in children, some are not.

Our mission here, our objective here is to really discuss these, even those that are in early phase testing, to see what's next and to seek your advice and input into how the agency might formulate a written request to incentivize sponsors to evaluate and develop these in a more timely fashion, if and when appropriate.

Tomorrow afternoon, we'll have a general discussion on a topic of considerable interest and some controversy, sort of at the crossroads of personalized medicine and ethical evaluation of

specific research procedures, but this one actually involved in selection of personalized therapeutic approaches in diffuse intrinsic pontine glioma.

Again, thank you. We appreciate you being here. We appreciate your frank questions and insight and look forward to a successful two days. Thank you.

DR. PAPPO: Thank you very much, Dr. Reaman. For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a 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 very much.

We will now proceed with topic 1, venetoclax from AbbVie Incorporated. Dr. Lauren Tesh will read the conflict of interest statement for this session.

Conflict of Interest Statement

DR. TESH: The Food and Drug Administration is convening today's meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are

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

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

FDA has determined that members and temporary voting members of this committee are in compliance with the 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 and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for 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.

This session's agenda involves information to gauge investigator interest in exploring potential pediatric development plans for five chemical entities in various stages of development for adult cancer indications.

The subcommittee will consider and discuss issues concerning diseases to be studied, patient populations to be included, and possible study designs in the development of these products for

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

The product under consideration for this session is venetoclax, presentation by AbbVie, Inc. This is a particular matters meeting during which specific matters related to AbbVie's product will be discussed.

Based on the agenda for today's meeting and all financial interest reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this session.

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

With respect to FDA's invited industry representative, we would like to disclose that Dr. P.K. Morrow is participating in this meeting as a non-voting industry representative acting on

behalf of regulated industry. Dr. Morrow's role at this meeting is to represent industry in general and not any particular company. Dr. Morrow is employed by Amgen.

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

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

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

an individual's presentation.

For this reason, the FDA encourages all participants, including the sponsor's nonemployee 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 interests in the sponsor, including equity interests and those based on the outcome of the meeting.

Likewise, 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 the sponsor's presentation.

Industry Presentation - Su Young Kim

DR. KIM: Thank you very much. Good morning. My name is Su Young Kim. I'm a medical director with the venetoclax program and a

pediatric oncologist by training.

We are here to present our proposal for the development of venetoclax in pediatric patients with select relapsed or refractory cancers. Everyone who has treated these patients knows how poor the prognosis is. I thank you for the opportunity to discuss our proposal.

Here is the agenda for today's presentation. I will begin with the regulatory history of venetoclax, then describe the mechanism of action and how we utilize that mechanism to identify pediatric tumor types that have the highest potential for response.

I will briefly review our clinical trial experience in adults, detail our proposed pediatric plan, and then move on to a discussion of the challenges that we have identified.

AbbVie filed the investigational new drug application to the FDA in 2010, followed by treatment of the first patient in June 2011. We received orphan drug designation in three indications, and also three breakthrough therapy

designations.

Most recently, venetoclax gained accelerated approval in April for patients with relapsed or refractory CLL who have 17p chromosome deletion.

Venetoclax is a novel, orally bioavailable, small molecule, B-cell lymphoma 2 inhibitor that binds selectively with high affinity to BCL-2 and with lower affinity to other anti-apoptotic family proteins. Overexpression of anti-apoptotic proteins is associated with tumor initiation, disease progression, and increased resistance to chemotherapy.

BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins. Venetoclax binds with high affinity to BCL-2, freeing up pro-apoptotic proteins to initiate apoptosis and activate caspases, finally resulting in programmed cell death.

BCL-2 overexpression is detected in many malignancies, and with additional preclinical evidence, we can select indications that have a high probability of responding to venetoclax.

Let me present the clinical trial experience in adults. Our adult clinical program is global in scope, with more than 20 studies in various hematological malignancies.

We have observed monotherapy activity in all of the indications listed, but for brevity, I will only discuss findings in CLL, AML, and NHL. Of note, all of the efficacy and safety data presented are from single-arm trials.

The accelerated approval of venetoclax for patients with 17p deletion CLL was based on a phase 2 study that showed an overall response rate of 80 percent and a complete response rate of 7.5 percent in this hard-to-treat population.

Single-agent activity was observed in patients with AML, shown in the middle column, with a response rate of 19 percent and a complete remission rate of 6 percent.

These promising findings resulted in an initiation of several combination studies, one of which included low-dose cytarabine. This combination led to an improvement in objective

response rate to 44 percent and an increase in CR rate to 22 percent.

Here, you see the data demonstrating activity of venetoclax in many subtypes of NHL, both as monotherapy and in combination with bendamustine and rituximab. We observed high responses in many subtypes in NHL, but I would like to focus on diffuse large B-cell lymphoma, which is the most common subtype of NHL in adolescents.

Venetoclax monotherapy had a response rate of 18 percent, with 10 percent achieving complete remission. Both overall response and complete remission rate increased when venetoclax was given in combination with bendamustine and rituximab. In all of our venetoclax adult studies, we have observed a consistent and manageable safety profile which should translate to the pediatric population as well.

Looking at the overall exposure with venetoclax, approximately 1500 patients received venetoclax in oncology trials, the majority of whom had CLL.

Patients received venetoclax as part of combination therapy or monotherapy. Of the 560 patients treated with monotherapy, 50 received treatment for over 2 years, and more than 200 patients received treatment for more than 1 year across all indications.

Here is the overall safety profile in adult patients. The most common adverse events across the venetoclax monotherapy studies were mild GI toxicities. The most common grade 3-4 adverse events were cytopenias, which is not unexpected since all of the patients had relapsed disease.

Additionally, I'd like to discuss the identified risk of tumor lysis syndrome and neutropenia. The most common adverse events were mild nausea and diarrhea. This data includes patients with the most recently approved CLL indication, as well as patients with AML and NHL, who are the most relevant to the pediatric population.

The most common grade 3-4 adverse events were cytopenias, much of which is consistent with

their underlying diseases. Importantly, most events were managed with standard of care and did not require coming off study.

The potent activity of venetoclax can lead to a rapid reduction in tumor burden, so there is a risk of developing tumor lysis syndrome. Clinical tumor lysis was observed only in early dose-finding studies in CLL patients with high tumor burden.

Since then, TLS has been mitigated by a more gradual dosing ramp-up which allows for slower tumor destruction. Standard prophylaxis measures are also strongly recommended. Since December 2012, no cases of clinical TLS had been observed.

Neutropenia is a common grade 3-4 adverse event in the monotherapy studies, but many times, it's difficult to distinguish from the underlying disease.

These events have been managed with standard of care treatment, including the use of growth factors and also by interrupting or lowering the dose of venetoclax. The vast majority of these events improved over time on study, and,

importantly, there was no trend toward increased infection rate.

The following safety parameters have been considered for the pediatric study. The safety profile is well-characterized for adults, and we believe it should be similar for children. No additional safety concerns have been identified among the 50-plus patients who continued to receive venetoclax for over 2 years.

A relevant nonclinical finding in adult animals is decreased spermatogenesis. However, the risk to humans is unknown. In all venetoclax studies, sperm banking is advised.

We are testing venetoclax in a nonclinical juvenile toxicology study in order to better to characterize the potential safety profile for the pediatric population.

Now, let's turn our attention to our proposed pediatric plan. We assessed the 25 most common pediatric cancers for potential response to venetoclax. The following three criteria were all required for pediatric development: BCL-2

overexpression, response in cell lines, and also response in murine xenograft models.

These four tumor types, AML, NHL, ALL, and neuroblastoma fulfilled all of those criteria. In addition, for AML and NHL, we have already seen clinical responses in adults.

Here is just one example of a murine preclinical study utilizing a neuroblastoma patient-derived xenograft. Shown in gray are control mice treated with vehicle alone, who all succumbed to tumor progression.

In orange are mice treated with cyclophosphamide and in blue are mice treated with venetoclax, all of which have prolonged survival, including 10 to 20 percent who have long-term survival. Shown in green are mice treated with a combination of venetoclax and cyclophosphamide, showing that more than half of the mice remain free of disease.

The venetoclax pediatric program was developed to address the high unmet medical need for patients with these select tumor types. For

ALL, NHL, and neuroblastoma, intensive multimodal therapy has resulted in excellent overall survival rates of over 75 percent for newly diagnosed patients. For AML, overall survival remains around 60 percent. Unfortunately, in the relapsed/refractory setting, prognosis remains quite dismal for all of these indications, and thus represents a significant unmet medical need.

I will now review our proposed pediatric study design. We have had many discussions with the leaders of both the Children's Oncology Group in the United States and the Innovative Therapies for Children with Cancer Consortium in the European Union, who have all contributed to the study design and specifics.

This is a phase 1, multicenter, global study with 40 sites that will enroll approximately 150 patients age 1 to less than 18 years. The primary objectives will focus on safety and pharmacokinetics. Secondary objectives will assess efficacy in the monotherapy setting and safety in combination with chemotherapy.

Exploratory objectives will include minimal residual disease status when applicable and biomarker analysis to try to answer two questions. First, can we identify patients who will respond to venetoclax; and, second, if patients progress, can we determine the mechanism of resistance in order to inform future trials?

Our phase 1 single-arm study will be conducted in two parts. During part 1, dose escalation, we will use a standard 3-plus-3-plus-3 design. Patients will receive daily ramp-up dosing of venetoclax up to 400 milligrams in dose level 1 and up to 800 milligrams in dose level 2 to determine the recommended dose for part 2 of the study. During part 2, cohort expansion, enrollment into each of the four cohorts will be expanded to a maximum of 25 patients per tumor type.

During the dose escalation part of the study, patients will be separated by indication due to differences in bone marrow involvement, and thus, the use of different DLT criteria. Those with AML or ALL will be in one group, and those

with NHL or neuroblastoma will be in another group.

Patients will also be stratified by weight, thus resulting in four unique dose escalation groups. Patients who weigh greater than or equal to 20 kilograms, for both groups, will be enrolled in dose level 1. Once that dose level is cleared, the next set of patients will be enrolled in dose level 2. Concurrently, patients who weigh less than 20 kilograms can enroll in dose level 1.

The groups will enroll sequentially so that PK and safety data from the higher-weight groups can inform the dosing in the lower-weight groups.

For part 2 cohort expansion, we will utilize the Gehan 2-stage design per tumor type to minimize the number of patients enrolled in stage 1 if patients do not have a response.

Eight patients will be enrolled initially for each tumor cohort. If no patient has a response, then enrollment into that specific cohort will end due to the low probability that we will reach the desired response rate.

On the other hand, the number of patients

who respond from the first stage will determine how many additional patients can be enrolled in stage 2, up to a maximum of 25 patients in each cohort. We are targeting a response rate of 20 percent for each tumor cohort.

Two formulations of venetoclax will be available for the pediatric study. The recently approved 10, 50, and 100-milligram oral tablets will be used for children who are able to swallow tablets. Rapidly disintegrating tablets of 2.5, 10, and 25 milligrams will be available and can be used to make an oral liquid suspension for children who are not able to swallow tablets. The pediatric doses will be based on modeling of adult PK data.

The dosing for pediatrics was discussed with members of COG and ITCC, because this is a key component to the safety of venetoclax in children. Age has a significant impact on intestinal and hepatic CYP3A maturation during the first two years of life. Therefore, we are proposing age band dosing in patients less than two years of age and weight band dosing for those who are two years of

age and older.

Available formulations will allow adequate dose escalation and dosing to the desired exposure based on PK modeling. This dosing ramp-up scheme is assigned to deliver the lowest toxicity, while maintaining the responses observed in the adult studies.

Here, you see the simulated exposures at steady-state of venetoclax. This figure is illustrative dose level 1, dose level 2 with double these doses. The projected doses are listed on top of the bars. The pediatric doses are projected to match exposure equivalent to the adult CLL dose of 400 milligrams to ensure similar safety and efficacy.

For select patients, venetoclax will also be allowed in combination with chemotherapy. Each patient must have an acceptable safety profile with monotherapy and must also meet the efficacy endpoint, after which patients can have the option of receiving chemotherapy in combination with venetoclax, based on the investigator's discretion

of what is in the best interest for the child.

The rationale for combination is that treatment with a cytotoxic agent may push a tumor cell that is prime to undergo apoptosis over the edge. Combination therapy may also help some patients maintain their clinical response and help others who show progression after response.

For patients appropriate for combination therapy, the following agents will be allowed per indication. All of these agents have shown synergy in preclinical studies, and they have also demonstrated an acceptable safety profile in adult venetoclax phase 1 and phase 2 combination trials. Of note, all of these agents are a part of salvage therapy regimens in these indications.

There are some challenges when developing a pediatric trial in this space. First, to mitigate the challenges around making a palatable liquid formulation, we have conducted human taste studies. Additionally, a follow-up study is ongoing to evaluate dosing vehicles.

At high body weights and dose bands, the

total number of tablets could be a challenge, and in those cases, a combination of tablets and liquid dosing may be an option. The food effect on the pediatric formulation is unknown, but will be assessed in the upcoming bioavailability study.

Also, enrolling patients with NHL and diffused large B-cell lymphoma will be a challenge simply due to the low prevalence in the pediatric population. In attempts to mitigate this challenge, we will conduct outreach to encourage screening.

Despite other ongoing trials in ALL, AML, and neuroblastoma, we don't believe recruitment will be a challenge for these populations based on the differential inclusion criteria and lack of a curative option.

In summary, venetoclax has promising activity in adults, with an acceptable and consistent safety profile across various hematological malignancies. We have identified four tumor types in children that have a high probability of response based on available

preclinical and clinical evidence.

In the relapsed and refractory setting, morbidity and mortality remains high in these settings. In certain malignancies, such as AML, effective treatment options are limited. In others, such as ALL, other promising therapies exist, but mechanistically, venetoclax works differently than other therapies and may show response in patients where other treatments have failed.

Because we are focused on treating relapsed and refractory patients, venetoclax will offer another treatment options to children with select cancer types.

The sponsors, AbbVie, Genentech, and Roche, are committed to developing venetoclax in the pediatric population. Thank you, and we look forward to your questions and discussions.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you very much, Dr. Kim. We will now take clarifying questions for the sponsor. Please remember to state your name for

the record before you speak. If you can, please direct your questions to a specific presenter.

Dr. Adamson?

DR. ADAMSON: Peter Adamson. Thank you for that presentation. This is more of an advice than a question, but I'll work a question into that. Dose-finding in children with hematologic malignancies is generally something we don't pursue. There's a very high inevaluability rate because of the rapid progression of the disease, and, historically, we have found it really uninformative to try to seek out a separate dose when there's an opportunity to define the dose in patients with solid tumors.

I think your strategy to identify a dose in a relapsed leukemia population is probably not an ideal strategy. I think you can successfully do that in the neuroblastoma population and then readily carry that dose directly into phase 2.

I suspect what you'll find is just a very high inevaluability rate from the inability for the majority of patients if you're projecting a

20 percent optimistic response rate. That means likely 80 percent of your patients won't complete a single cycle of disease, and therefore will be inevaluable. So that would be an area of caution as far as developing this, but, rather, it's a straight -- get your dose in solid tumors and go straight to your phase 2 two-stage component.

I do think it is going to be challenging outside of the leukemias to move into the lymphomas given the frontline cure rates. However, again, one can pursue that, with the recommendation of going straight into phase 2.

I would also just want to clarify the decision to go with a banding dose, which is reasonable -- but you have a lot of formulations, which is great as far as dosing. And, generally, we've managed that with per-kilo dosing and then just having a table of what the dose actually is.

I think your dosing, if I understand, ranges from probably 6 to 9 mgs per kg at the starting dose if you look across the ages. I was wondering why you just didn't decide and land on a

single -- if it's going to be 8 mg per kg and just use your formulations to come as close to nominal as possible.

DR. KIM: Thank you very much for that comment, for the first comment, and we will take that into advice.

Dr. Shebley can answer the second part of the question for you.

DR. SHEBLEY: Mohamad Shebley, associate director of clinical pharmacology.

We did consider the per-kilogram dosing and, essentially, what we have are the band dosings to consider the weight differences across these age groups. You're right, it's about 6 to 7 milligrams per kilogram is what it essentially will come down to.

DR. PAPPO: Steve?

DR. DuBOIS: Steve DuBois, Dana-Faber. Thank you, Su.

A couple of questions about the stage 2 design. Would a response in combination with chemotherapy count as a success or you're only

looking for monotherapy success for the two-stage design?

DR. KIM: It's only monotherapy that we're counting efficacy.

DR. DuBOIS: Then for the combination with chemotherapy, you're requiring several stable disease evaluations before allowing patients to move on to combination therapy. Based on I think where you'd be going with this agent, and also based on the preclinical data of higher response rates with combination, the rationale for having a patient with stable disease just continue on monotherapy wasn't really clear to me.

DR. KIM: It wasn't clear because we're still working out the specifics of that. The advisors we've talked to have made it clear that the patients who are responding, we really do have to do something.

The best case scenario is patients who are approaching CR and have a transplant option. That is the only curative option at present. So we are almost compelled to do whatever we can to give them

limited venetoclax until they get to their transplant.

Same thing in patients who reach CR. Once you get to CR and you don't have a transplant option, then there's also the possibility that you may relapse on monotherapy alone. And in those cases, also, once you've reached CR and declared your response, then we will allow the option of receiving chemotherapy, again, if the investigator thinks it's in the best interest of the child.

The patients with PR, also we will allow to get chemotherapy, with the rationale that once you achieve PR, the chemotherapy may just push you over where you will reach that CR status and go to transplant, if you have that option.

The other group of patients is PD patients, and then apparently at any time after they clear their PD, then you'll also have the option of going to chemotherapy.

The part in the middle, the ST patients, we're still trying to decide how long we wait because they have stable disease. They're not

progressing rapidly is the good thing. But we do believe at a certain point after two or three, depending on the disease, stable diseases, you should begin the opportunity again to deepen your response.

DR. PAPPO: Dr. Weigel?

DR. WEIGEL: Brenda Weigel. I am wondering, in regard to the heme malignancies, particularly the leukemia, that as a single-agent, again, unlikely to really be able to answer that question due to the progressive nature of the disease, meaning combinations potentially are going to be very important.

Have you looked at any sequencing issues? Because with BCL-2 inhibition, sequencing with different agents, particularly cytotoxics or agents with different mechanisms, might be very important with regard to how you combine drugs and how you look at optimizing the use of the agent in combination.

DR. KIM: We are starting some of that in our adult trials also, where we do realize that

timing is important depending on the circumstance.

We are trying to explore this in our preclinical setting where we have murine models that we know are effective. In that case, we would like to answer actually several questions. What chemotherapy is best? Are there other novel agents that work better in combination with venetoclax; and if so, then is there a sequencing that you have to follow to make that more successful? We hope to have those answers soon.

DR. PAPPO: Dr. Warren?

DR. WARREN: Hi, Su Young. This follows a little bit on Peter's comments earlier.

First of all, I applaud you for trying to look at different subgroups in the pediatric population as far as age and metabolism goes. As you know, there's no standard cutoff or no standard way to do this, whether we use age 21 in pediatrics or 18. We sometimes look below age 12 and over age 12.

Is there any pharmacokinetic data from the adults that would make us think that we need to

look at adolescents versus younger children in addition to the 20-kilo weight loss?

A second question is, do we know the CNS penetration of this agent for children who may have CNS leukemia?

DR. KIM: I'll let Dr. Shebley answer the first question. As he's coming up, the second question, CNS penetration is very low. We were hoping that it would be effective for brain tumors, but if we are to pursue this in brain tumors, then we'd have to do a lot more modeling and a lot different formulation to try to make it more effective.

DR. SHEBLEY: Mohamad Shebley. To answer that the first part of the question, we don't have adult data to show the age effect, for example. However, due to the metabolism of venetoclax, which it is established to be via CYP3A4, and the well-established literature suggesting the ontogeny effect on the maturation, we considered the age-based dosing in the younger groups, up to 2 years old. And beyond that, it's just an element

or scaling function based on body weight, the projected is.

DR. PAPPO: Dr. MacDonald?

DR. MacDONALD: Tobey MacDonald. Given the molecular diversity of these diseases, do you have any data about whether the expression of BCL-2 is associated with any particular molecular phenotype and/or response to these agents associated in either the preclinical or clinical, in the adult or pediatric preclinical models to define your target population?

DR. KIM: Most of our data comes from the ALL realm where there are distinct subtypes. We do see very potent response, at least in animal models, for subgroups of ALL that do really poorly. So ETP-ALL, 17-19 translocations, the MML, ALL. We do have differential responses.

It doesn't mean that if one is poor, we just see higher levels of BCL-2 expression and more profound responses when we do the murine models. But we don't think that that's a reason to actually restrict the rest of the ALL group. So we are

doing a broad study to allow all patients, no matter the subtype of ALL, to enroll. And then with our biomarker analysis, we hope to tease out the patients that we can predict will response to venetoclax in future trials.

DR. PAPPO: It's my turn to ask the question. Alberto Pappo.

(Laughter.)

DR. PAPPO: I have a couple of questions. What is the difference in the mechanism of action of this agent with other BCL-2 inhibitors that have been tried in the past?

DR. KIM: This is the first specific BCL. It's the first of novel specific BCL-2 inhibitors. We have developed a compound called ABT263, which is a more broad spectrum. In addition to BCL-2, you also have BCL-XL inhibition.

What we found in those cases is that you do have thrombocytopenia in the clinic. So for those, we've limited the indications to more of the BCL-2-specific indication.

DR. PAPPO: The other question I had is on

the patients that develop pneumonia, was this a pneumonitis, or was this an infectious complication, or was this during neutropenia, or is there more information about that?

DR. KIM: No, it was not a pneumonitis. It is in the elderly population. Most of our patients have CLL. They are immunocompromised, to a certain degree, to start with, and so we have seen pneumonia in that setting.

Sometimes the adverse event of pneumonia can be anywhere from a real pneumonia to some upper respiratory tract infection. But we have not seen any pneumonitis in the setting.

DR. PAPPO: A couple of very quick questions, and then there's a whole list, I promise.

The other thing is on the design of the phase 1, why did you split it by weight so patients less than 20 kilograms will get their first dose level or you've identified -- after you start dosing patients with more than 20 for dose level 2, if the major determinant of the PK of this agent is

age and not weight?

DR. KIM: I'd like to have Dr. Shebley answer that question.

DR. SHEBLEY: Mohamad Shebley. Basically, we did consider the different age groups originally where we had zero to 2, 2 to 6, 6 to 12, and 12 and beyond, as an age banding. However, we later on realized that will take a long time for enrolling all of these age groups.

Since we have body weight as an effect on clearance for venetoclax, we decided to use the weight banding. The 20 kilogram really is a reflection of approximately 5- to 6-year-olds, where we think those patients from 6-year-old and above will be able to swallow the adult tablets, that we have relatively better confidence in projecting the clearance and the PK in those patients. This way, we will use those data first to inform the lower weight groups and the lower ages.

DR. PAPPO: Thank you. The final question I have is a follow-up to Dr. DuBois' question.

Patients that have had this single-agent, they have to achieve a CR or a PR in order for them to be eligible to continue with the combination chemotherapy, or is it only after they progress that you're allowed to add chemotherapy to the agent?

DR. KIM: After they are declared CR, PR, or PD.

DR. PAPPO: Either of the three.

DR. KIM: Either of the three.

DR. PAPPO: Okay. Thank you. Dr. Seibel?

DR. SEIBEL: I believe in your briefing document, you mentioned something about looking at some of the rarer tumors, such as clear cell sarcoma and Wilms. Do you have data about activity?

DR. KIM: We do not. What we've seen is a high level BCL-2 expression, but more importantly to us, we see both high level BCL-2 expression and low levels of BCL-XL expression and the greater that ratio is, we think that you'll have a higher chance of responding to venetoclax.

These are rare tumor types. We have identified investigators in academia who have these cell line and murine models, and we're just waiting for the CDA to clear it before we can have them test venetoclax in the cell line and murine models.

DR. PAPPO: Dr. Morrow?

DR. MORROW: You talk about the response rates with combination therapy with venetoclax. The question for you is given the adverse event profile, what was the dose intensity with the combination with other chemotherapies when providing venetoclax?

DR. KIM: Dose intensity, it depended on the trial and what the combination chemo was. The venetoclax dose we try to keep standard as much as possible to that specific indication.

Sometimes the first thing we would change is either decreasing the venetoclax dose or decreasing the chemotherapy. Did you want specific numbers? So low-dose cytarabine was at 20 milligrams per kilogram.

DR. PAPPO: Dr. Armstrong?

DR. ARMSTRONG: Your approval in CLL was for patients was 17p deletions. I'm wondering how common either 17p deletions or p53 aberrations are in the diseases that you're targeting and whether or not that might impact the efficacy of this.

DR. KIM: That may. There are ALL, AML -- all of these disease types, there are a certain percentage that have p53 mutation or deletion. We don't know how that's going to impact yet, but I think that's what we like to focus our biomarker plan on to see what percentage of patients have these distinct changes, not only p53, but all the other genetic changes in ALL and AML do a systematic approach and then at the end, try to correlate with response.

DR. PAPPO: Dr. Reaman?

DR. REAMAN: Thanks. I have a couple of questions. Could you elaborate a little bit on the biomarker studies that you plan? In the adult series, have there been any correlations between BCL-2 expression and response?

DR. KIM: The first part of that question,

we are planning extensive biomarker evaluation, knowing that the sample size is going to be low. So we are going to try to prioritize what we think are the biggest-bang-for-the-buck studies at the top and moving all the way to the bottom, depending how much sample we can collect.

We will collect bone marrow, blood, and tumor tissue, if we can, if there's a clinical indication to obtain sample at that point.

What we'd like to do is start with a molecular diagnostic subtype testing, cytogenetics, FISH, mutational profile, move on to BCL-2 family expression profiling either by immunohistochemistry or by flow cytometry, and then do some tumor genomics using RNA sequencing.

Then minimal residual disease, we're still trying to determine if it's best to have the individual sites do it, because it's so much of a component of the standard of care for the child now, or if we should do it centrally or have a central vendor test that.

The other example is if we have enough

sample available, it would be mitochondrial priming or BH3 profiling and then single-cell protein profiling.

DR. REAMAN: The combination studies, in addition to achieving complete response, we're frequently interested in the durability of responses. By adding a combination agent after achieving complete response, how do you propose to assess durability when adding a second agent?

DR. KIM: It's a trade-off. We originally had those endpoints built in, DOR, PFS, and OS, and then what we heard from the investigators was that this was not in the best interest of the child and we should add chemotherapy at the first opportunity we can.

It will, obviously, change how we analyze DOR, because DOR for monotherapy, at that point, may be 21 days. But that really doesn't reflect how well the drug is doing for the patient.

I think we're going to stick with our primary objectives, and we'll either have to censor patients or just do it as analysis

separately for patients who are on chemotherapy, do a separate analysis.

DR. REAMAN: I wasn't 100 percent sure, but you have a fixed combination that patients are permitted to receive or is it investigator choice?

DR. KIM: It's not investigator choice. We can probably get that slide back up. We have identified several agents that we think are going to be effective based on preclinical evidence and also what we've seen in adult realm.

We're still working with investigators at COG and ITCC to determine if this is the best agent that we should add on to venetoclax, both clinically and scientifically.

The rationale for what we did so far is that we do have safety data for low-dose cytarabine for adult patients with AML. We know the safety profile and the dosing that's going to be tolerable in that setting.

Same thing with NHL, we've had combination studies with rituximab plus venetoclax. The ALL, we think dexamethasone and vincristine and

neuroblastoma cyclophosphamide will minimize the side effects that they may experience compared to using a standard salvage regimen, venetoclax in combination with a standard salvage regimen.

DR. REAMAN: I would just encourage you to keep it as standardized as possible and to really think about the durability of response issue.

Then the last question, other than the inhibition of spermatogenesis, were there other toxicities that you saw in your adult experience that makes you think that juvenile animal studies are needed? Because you really have a large number of adults who have had significant exposure to this agent.

DR. KIM: I'd like to have Dr. Rhodes, who ran these studies, answer that question.

DR. RHODES: Bill Rhodes, nonclinical toxicology, AbbVie.

We have conducted nonclinical toxicology studies in dogs, rats, and mice. We observed testicular germ cell decreases. This was limited to dogs. But we have also observed decreases in

lymphocytes and decreases in hemoglobin, which have been reported in adults as well.

We had a couple of other non-adverse findings, one of which was increased amount of white hair, due to loss of pigmentation in the hair, which we think is a mechanistic effect.

We also had minimal to mild single cell necrosis in various epithelial tissues.

DR. PAPPO: Thank you. Dr. Adamson?

DR. ADAMSON: Two questions. As you know, in pediatric oncology, tumor lysis is a desired endpoint, and we would never manage it with ramp-up; we would just prevent it.

I see you are mirroring the adult experience with ramping it up. Are you planning to do that in patients with neuroblastoma, also?

DR. KIM: We don't know what we're going to see in neuroblastoma. Preclinically, neuroblastoma -- aside from CLL, where the BCL-2 expression level is just super high, the next tumor type that we see on the scale is neuroblastoma.

We are being conservative, assuming that

patients with neuroblastoma may have tumor lysis, also. So we will ask those patients to be hospitalized, also, with a dosing ramp-up daily.

DR. ADAMSON: As you know, that's an interesting assumption in neuroblastoma.

With that said, the downside of doing this is you're going to have the first cycle of patients who only receive full dose for 9 days. That is not going to give you a good estimate of tolerance to that dose, and you're going to lose an increasing number of patients to progressive disease. I would advise against that approach in dose finding, especially in solid tumors, which would become a New England Journal paper, if you see it, rather than a standard appropriate.

My other question is, do you have an agreed upon PIP?

DR. KIM: We are submitting that probably in the next month or two.

DR. ADAMSON: Will these discussions have a substantive influence on what gets submitted with your PIP?

DR. KIM: Definitely, yes.

DR. ADAMSON: Okay.

DR. PAPPO: Dr. Glade Bender?

DR. GLADE BENDER: Dr. Adamson just covered one of my issues, which was the ramp-up and the DLT window being only 21 days.

I wonder, have you treated any solid tumors in adults, and, if so, what was the median time to any sign of response as related to adding in the cytotoxic agent?

DR. KIM: It would actually depend on your definition of what solid tumors are. If you include the NHL as more of a solid tumor than a liquid tumor, then we have seen responses in NHL patients.

It really depends on the subtype of NHL also. For diffuse large B-cell lymphoma, we've seen response as soon as the first staging, the first protocol-defined staging evaluation, which was either 8 weeks or 12 weeks, depending on the protocol.

In our combination studies, after the

initial ramp-up, if there wasn't a ramp-up for that disorder, then we'd start combination chemotherapy right away. We don't have much data in terms of how fast the combo acts compared to the monotherapy.

DR. GLADE BENDER: I imagine that is the kind of response you're going to get in neuroblastoma.

I also wanted to echo the idea of doing a more generalized phase 1 dose escalation in solid tumors. I think that would also give people the opportunity to put relapsed Wilms tumor and clear cell sarcoma of kidney patients on study, because those are terrible diseases, if they recur. Granted, they are rare.

In the past, we have allowed for rare diseases to have a strata even if -- but it won't hold up the study if it doesn't fully enroll, because I think that this would be of very interesting agent for those tumors. I wouldn't hold it up for preclinical data either. I'd go right to the clinical experiment.

DR. KIM: Thank you.

DR. PAPPO: Dr. Brown?

DR. BROWN: Thanks. Pat Brown. Just one clarifying question. In figure 2 of the briefing document, it appears that a patient just below or just above the 20-kilogram mark would have a 100 percent difference in their dose, at least to start with, and up to 60 percent even at the final dose; is that right?

DR. KIM: I think this is the wrong figure. You can go one --

DR. BROWN: I was looking at the FDA briefing document. It's the table of dosing in dose level 1 and dose level 2.

DR. KIM: I'll have Dr. Shebley answer that question while we're waiting.

DR. SHEBLEY: I believe we need the dosing table.

DR. BROWN: If you're 19.9 kilograms, you get 5 milligrams. If you're 20.1 kilograms, you get 10 milligrams. That's a 100 percent difference to start with.

DR. SHEBLEY: Sorry. Mohamad Shebley. Yes. We based these cuts basically on taking the average of weights in each band.

DR. BROWN: Right.

DR. SHEBLEY: Given that we know there is a high variability in the PK of venetoclax, as shown on this slide, the exposure would overlap whether you are at that cusp of the band.

DR. BROWN: The follow-up is, are there precedents for pediatric dose-finding studies with that sort of variability in dosing over such a small weight difference?

DR. KIM: I'm going to ask Dr. Shebley to come back up.

(Laughter.)

DR. SHEBLEY: Mohamad Shebley. I'm not sure I have an example to mention. Again, when we collect the data in phase 1, we'll be able to determine if that weight and age has the impact on the PK to inform the dose.

DR. BROWN: The sample size will be limited in those kind of subgroups, but it's good to try

that.

The second question I have is -- well, more of a statement. In leukemia, it has been extremely difficult to accrue to single-agent studies with anticipated single-agent response rates in this rage. They basically have not been able to accrue.

To echo the sentiments that Dr. Adamson initially brought up, I think attempting to do a leukemia or even a lymphoma study with a single agent with an anticipated response rate in the 20 percent range is very likely to demonstrate poor accrual to the point where it won't be possible.

DR. PAPPO: Thank you. Dr. DuBois?

DR. DuBOIS: Steve DuBois, Dana-Farber. Just to follow up on the combo question in heme malignancies, you're including patients with NHL, which can be T-cell or B-cell, but the combination is with rituximab, which shouldn't really be relevant with a T-cell lymphoma. Then for the ALL and AML, given the lack of CNS penetration, I think consideration for allowing intrathecal chemotherapy would be an important consideration.

DR. KIM: Depending on the subtype, we may actually refine that list for combination chemo to give what makes sense in the setting. We will allow intrathecal therapy for patients with AML and ALL.

DR. PAPPO: Thank you. Are there any other questions? Dr. Adamson?

DR. ADAMSON: Just a comment. These comments, I think, reflect that everyone around this table wants this trial to be a success, so they should be taken in that light.

We're very pleased that you're here and committed to pediatric development. We just want to do our best to assure the success of this early study.

DR. KIM: Thank you.

DR. PAPPO: Any other questions?

(No response.)

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

DR. KIM: Thank you.

Questions to the Subcommittee and Discussion

DR. PAPPO: There are no OPH speakers. We

will now proceed with the questions to the committee and panel discussions.

I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We will start with the first question.

DR. EHRLICH: Please address the biologic significance of BCL-2 inhibition as a treatment strategy in malignancies in children.

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

DR. DuBOIS: I can just speak to neuroblastoma, where the community is quite interested in this agent. I'll point out a recent high impact publication evaluating BCL-2 inhibition in combination with aurora kinase inhibition, showing very nice preclinical activity. In neuroblastoma, there's certainly enthusiasm.

DR. PAPPO: Dr. Weigel?

DR. WEIGEL: I would say, in general, BCL-2

inhibition has been of interest in pediatric oncology for a while. I think the real challenge is how do we optimize inhibition of the target. I think this is a drug certainly hitting that pathway, and I think optimizing it with combinations and the strategies and the discussion we've just has is going to be very, very important. But I think it is applicable to many pediatric cancers. I think it's an important marker.

DR. PAPPO: Anybody else?

(No response.)

DR. PAPPO: To summarize this first question, there appears to be enthusiasm from the panel in proceeding with the study of this drug. There's specific enthusiasm in neuroblastoma from preclinical data.

The trick is going to be to optimize how you basically design the study to optimize the likelihood of this drug being moved into clinical trials and to identify the relevant subtypes that this drug should be implemented in.

Just to add a little bit more, as to the

previous discussions, also to try to take into consideration the design of the study based on the remarks that were made by Dr. Bender and Dr. Adamson, specifically in leukemia.

Any other things that I missed or anything else?

(No response.)

DR. PAPPO: Good summary? Yes.

(Laughter.)

DR. PAPPO: We will now proceed to the second question.

DR. EHRLICH: Please address any short term and potential long-term or late toxicities that may be associated with the use of this drug in children.

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

Dr. Adamson?

DR. ADAMSON: I would just circle back. I think given the nature of relapsed and refractory childhood cancers, maximizing the likelihood of at

least defining the short-term toxicities by doing the evaluation, as was suggested, potentially in a broader -- during the phase 1 evaluation, in a broader solid tumor population, I think, is probably going to give you the best information on the short-term tolerability of the doses, ideally with avoiding the ramp-up phase.

I think, as others have said, for leukemia, it gets more complex, because the need to move to combination therapy is much greater in order to get children through periods of evaluability. Obviously, we would be eager to learn longer-term toxicities, which will be based on the efficacy of this. But shorter-term, there's great potential to answer it in this study.

DR. PAPPO: Thank you. Any additional questions?

(No response.)

DR. PAPPO: To summarize, I think that it is important to better define the short-term toxicities of this therapy, and this could be optimized by including a broader population of

patients with solid tumors. That would give us a better idea of the short-term toxicities of this agent.

Of course, if we have the opportunity to evaluate long-term toxicities in patients that have good response, that would be great. Also, using the ramp-up phase dosing of the study would likely not allow us to get the full spectrum of toxicities on these patients, at least during the first cycle of therapy.

Any additional comments, or suggestions, or questions?

(No response.)

DR. PAPPO: We will now move to the third question.

DR. EHRLICH: Please address whether sufficient relapsed or refractory patients would be available for evaluation of this drug given the numerous salvage therapy trials in progress.

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

MS. McMILLAN: I just want to make sure I understand completely that this new agent will be offered in addition to, but not instead of existing salvage therapies.

DR. PAPPO: Anybody want to tackle that?

MS. McMILLAN: That's from the patient perspective.

DR. ADAMSON: I think, in general, in this population, it's children who have run out of potential therapeutic options that would be eligible. Established salvage therapies, generally, will have been attempted before moving to this study.

That could change in a combination study with leukemia where it might be a very standard regimen with the addition of this. The answer is when there is an existing salvage therapy, it would likely be added. When there's no existing salvage therapy, it would likely be single-agent, and both would be acceptable.

MS. McMILLAN: Thank you.

DR. PAPPO: Any additional questions

regarding the number of patients available for evaluation for this drug?

Dr. Weigel?

DR. WEIGEL: I think this harkens back to comments made previously that the patient population, certainly in solid tumors, exists to really study this agent.

I think as a single-agent, there may be challenges for accrual as a single-agent, not because of limited necessarily in the leukemia population numbers, but of enthusiasm for a single-agent study. Numbers may be limiting in the lymphoma population just because of upfront cure rates at this point in time.

DR. PAPPO: Dr. Glade Bender?

DR. GLADE BENDER: I was going to say it's rarely a problem to find relapsed and refractory solid tumors. We have done trials in the past of a single-agent window followed by a combination to follow, which allows DLT collection of both single-agent and the combination. I think that might be a far more popular trial for solid tumors.

DR. PAPPO: Thank you. Dr. Neville?

DR. NEVILLE: Just to echo that, and also to say I think you should reconsider your combination choices, as discussed, because a lot of these agents the patients would've seen already. So you're competing against other new agents. I would say both a single-agent window with maybe not just another drug added, but a better combination, you'll get a higher accrual, in my opinion.

DR. PAPPO: Dr. Reaman?

DR. REAMAN: I think comment could be extended to the leukemias as well, and not just solid tumors. I would also suggest that this could be done internationally. If you're working with the EMA on a PIP, I think this is one of those situations where we're going to have to look at collaborating internationally and that's something that should be considered as well.

DR. PAPPO: Dr. Raetz?

DR. RAETZ: I agree with the statements that have been made about the concerns for a single-agent and the feasibility for leukemia. I

think there is some enthusiasm, though, for the rare subtypes, like the 17-19. So I just want to emphasize that that may be a particular population where there is as great enthusiasm.

DR. PAPPO: Any other additional comments, or questions, or suggestions?

(No response.)

DR. PAPPO: To summarize this, I believe that it should be considered that a study should include perhaps a window therapy, followed by combination therapy, to specifically target solid tumors; that it will be relatively difficult to do this in acute lymphoblastic leukemia and non-Hodgkin's lymphoma; to reconsider the combination choices that have been offered by patients both with leukemia and with solid tumors; consider an international collaborative study to increase the number of patients; and -- I don't know.

Is there anything else I missed or any other concerns or suggestions?

DR. BROWN: In the list of things that it

would be tough, I think you said ALL and NHL. I think AML would be included as well.

DR. PAPPO: AML. Thank you. If there are no additional suggestions, we will go to the fourth question.

DR. EHRLICH: Please discuss the design of the proposed phase 1 trial in children, including disease types and minimum tumor activity required for cohort expansion.

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

DR. WARREN: I think there should be a potentially separate phase 1 study for leukemia with a separate definition of dose-limiting toxicity, because I can't see how that would apply also to the solid tumor cohort.

DR. PAPPO: Thank you. Dr. Bender?

DR. GLADE BENDER: To build on Kathy's idea, I also think that to separate by diseases based on what you think is bone marrow infiltration may be the wrong approach. Advanced neuroblastoma can

have extensive bone marrow replacement, and so your hematologic toxicity interpretation would be just as difficult in that patient population as in the leukemias.

DR. PAPPO: Dr. Adamson?

DR. ADAMSON: I think we've discussed it probably earlier, but I would echo the recommendation from Julie in that in the solid tumor population, a design that we've used repetitively for these types of agents is cycle 1, single-agent; cycle 2, defined combination; cycle 1 getting the DLT PK tolerability; cycle 2 rolling right into combination. That's a design that's worked well and I think would work well in solid tumor.

In the hematologic malignancies, I think building on what Pat said, I would avoid dose-finding studies of single-agent because I think those are just going to be extremely difficult to do, but rather moving in with a reasonable dose potentially determined in the phase 1 and a design that might, out of the gate,

look at a combination in a relapsed setting. I think we can build on those two general principles, but not to try to accomplish in a single cohort, where ALL is going to potentially influence solid tumors and vice versa.

DR. PAPPO: Dr. Brown?

DR. BROWN: In terms of study design, I just would want to maybe mention that reconsideration of the dose determination schema in a banded fashion, there ought to be a little bit more consideration of other ways to do that just because of the just huge steps up and down in dosing over a very narrow weight ranges.

DR. PAPPO: Thank you. Dr. Weigel?

DR. WEIGEL: Also, in the section for study design and the points that have been brought up is to avoid ramp-up dosing that would limit the interpretation of toxicity in optimizing dose and go to a more straightforward dose-finding study.

DR. PAPPO: Dr. Neville?

DR. NEVILLE: Just to clarify, you mean with all diseases, right? Including --

DR. WEIGEL: With all diseases, solid tumor and leukemia.

DR. NEVILLE: Even leukemia?

DR. WEIGEL: Correct.

DR. NEVILLE: We have ways to prevent tumor lysis, so the ramp-up -- I agree with Brenda.

DR. PAPPO: Any additional comments?

(No response.)

DR. PAPPO: To summarize, we recommend that there would be a separate phase 1 study for leukemia and for solid tumors; also, to consider the design that has been done in the past for solid tumors, that is, to give single-agent during cycle 1 and then after the dose has been determined, to combine this with a series of agents or several agents during cycle 2; also, try to avoid a dose-finding study in hematologic malignancies; and, try to go straight to a trial that uses a combination in hematologic malignancies based on the dose that was determined on the phase 1 study in solid tumors; also, to reconsider the dose determination based on banding; and, to

avoid the ramp-up phase for all of the types of tumors, not only solid tumors, but leukemias, to facilitate interpretation of toxicity of the phase 1 study.

Any other issues or anything I missed? Yes, Amy?

DR. BARONE: I'd ask if anyone has any comments on the second part of that question. We talked mostly about the dose escalation. But on the cohort expansion, I think they mentioned 20 percent was the criteria for most tumor types, if everyone agrees with that as a reasonable percentage or activity estimation in this disease.

DR. PAPPO: Any comments on that?

DR. ADAMSON: A two-stage design, I think, is the right approach. Generally, we don't put the bar too high for the first stage, but the math works out.

Generally, our first stages are somewhere between 10 and 14 patients. And so I would work to see and make sure the bar isn't too high first stage, but second stage seems quite reasonable.

DR. PAPPO: Thank you. Yes, Dr. Warren?

DR. WARREN: I think part of this depends on the definition of response, which I'm not sure that we've reviewed at all, and if whether or not it includes minimal, a minor response.

DR. PAPPO: Any additional comments? Yes?

DR. WEIGEL: I think it's also going to depend on the disease that is being evaluated. So I think it may be different for the hematologic malignancies and first -- depending on the combinations and the way the study is designed.

I agree, for the solid tumors, I think this is a very reasonable bar.

DR. PAPPO: This is a reasonable design, and just to better clarify the definition of response for the different diseases. Any additional observations or comments?

(No response.)

DR. PAPPO: We will now move to the fifth question.

DR. EHRLICH: Please address the plans for administering venetoclax in combination with other

chemotherapy regimens.

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

Dr. Glade Bender?

DR. GLADE BENDER: When we move a phase 1 agent to phase 2, we often want to do it in the context of a randomized selection design, at which point we're placing that new agent on a backbone that we normally use.

I would suggest that one even consider that those standard backbones be the second stage of this, because the first question when you go to phase 2 is what is the toxicity of the new agent on top of the standard backbone.

We don't have that data, so we often have to pause after the first run-in. I wouldn't assume that people won't enroll because they may have already seen the agent. If this agent is novel and helps chemotherapy to work better by making the cells pro-apoptotic, then people may revisit the regimens that they've already seen.

DR. PAPPO: Be sure that this backbone will eventually be able to be used in a phase 2 and a phase 3 study.

DR. GLADE BENDER: Exactly. Then you'll also have the safety data, and it will ease the phase 2 study.

DR. PAPPO: Dr. DuBois?

DR. DuBOIS: I couldn't agree more with Julie. I mean I think the philosophy really should be not so much trying to cure patients with relapsed and refractory solid tumors and leukemias, but really how to rationally develop the agent to move this forward into an upfront regimen.

Toward that end, I think a combination with single-agent cyclophosphamide, I think, isn't really going to provide as much information perhaps as a combination with topotecan and cyclophosphamide that's used in combination for the upfront care, for example, in patients with neuroblastoma and also in other solid tumors.

I would encourage the sponsor to think about regimens or cassettes that might be moved upfront

and trying to obtain tolerability and efficacy data in that context.

DR. PAPPO: Thank you. Dr. Neville?

DR. NEVILLE: Just to agree with Julia and clarify what I said earlier, in the choices here, it's not just because they've seen the drug before, but I think one drug on top of single-agent cyclophosphamide in a relapsed or refractory neuroblastoma, I'm not optimistic about efficacy, and I would hate to see the drug killed because it wasn't on top of a robust enough backbone.

DR. PAPPO: Thank you. Any additional questions or comments?

(No response.)

DR. PAPPO: To summarize, then, to try to develop a more robust backbone to combine this agent where the chemotherapy that potentially will eventually be moved to either phase 2 or an upfront regimen, and so basically just to reconsider the drug combinations that you are proposing for the various diseases.

Any other suggestions or questions?

(No response.)

DR. PAPPO: Now, I think we have a break. One more question.

DR. EHRLICH: Discuss other relevant pediatric cancers, including clear cell sarcoma of the kidney and Wilms tumor, for which a biologic rationale for the evaluation of venetoclax exists with high BCL-2 expression in the absence of xenograft animal models.

DR. PAPPO: I don't have my little thing. If you think that the question has no issues, let's proceed with the comments. I lost my little thing over here.

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

Dr. Neville?

DR. NEVILLE: I think some of this has been covered. With the more aggressive rare diseases, there are a paucity of treatments available. And so I would encourage the sponsor where there is biologic evidence that this may have activity, to

open those cohorts, especially, as Julie said, in the phase 1.

I think clear cell and refractory Wilms, we've got nothing in other solid tumors where there may be activity.

DR. PAPPO: Julie?

DR. GLADE BENDER: Just to reiterate, those cohorts don't have to fully accrue for the study to close. If you saw response in 3 out of 3 clear cell sarcomas, that would be pretty convincing evidence that the drug was active.

DR. PAPPO: Yes, Steve?

DR. DuBOIS: Just to add my support. The figure 2 in the briefing document I think is really trying to tell us something about clear cell sarcoma of the kidney, where the BCL-2 to BCL-XL ratio is really much higher and much tighter than all of the other diseases, pediatric diseases presented.

I think we have precedent for these very rare but aggressive solid tumors, that if you build it, they will come. You can certainly, I think,

learn a fair bit even in an early phase trial.

DR. PAPPO: Thank you. Any additional comments or suggestions?

(No response.)

DR. PAPPO: To summarize, to try to consider expanding the number of histologies that are included in your solid tumor cohort, including patients, for example, with clear cell sarcoma.

Any additional comments or suggestions?

(No response.)

DR. PAPPO: I think we are done with the questions. We will now take a 20-minute break.

Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any members of the audience. We will resume at 9:45 in the morning. Thank you.

(Whereupon, at 9:22 a.m., a recess was taken.)

DR. PAPPO: We will now proceed with topic 2, tazemetostat from Epizyme Incorporated. Dr. Lauren Tesh will read the conflict of interest

statement for this session.

Conflict of Interest Statement

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

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

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of

interest laws.

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

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

and primary employment.

This session's agenda involves information to gauge investigator interest in exploring potential pediatric development plans for five chemical entities in various stages of development for adult cancer.

The subcommittee will consider and discuss issues concerning diseases to be studied, patient populations to be included, and possible study designs in the development of these products for pediatric use.

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

The product under consideration for this session is tazemetostat, presentation by Epizyme, Inc.

This is a particular matters meeting during which specific matters related to Epizyme's product will be discussed.

Based on the agenda for today's meeting and

all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Drs. Pappo and DuBois.

Dr. Pappo's waiver involves his employer's current interest with Epizyme for a study of tazemetostat, which is estimated to be between zero and $50,000 per year in funding.

Dr. DuBois' wavier involves his employer's two current studies of tazemetostat funded by Epizyme, which are estimated to be between $100,000 and $300,000 per year per study in funding.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on the FDA's website.

Copies of the waivers may be also obtained by submitting a written submission request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland,

20857 or a request may be sent via fax to 301-827-9267.

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

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

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusions will be noted for the record.

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

DR. PAPPO: Both the FDA 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 is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's nonemployee 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 interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, 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 the issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the sponsor's presentation.

Industry Presentation – Peter Ho

DR. HO: Good morning. My name is Peter Ho, and I'm the chief medical officer for Epizyme. On behalf of my colleagues, we'd like to thank the committee for the opportunity to present today our clinical development plan for tazemetostat for the treatment of pediatric patients with malignant rhabdoid tumors and other INI1-negative tumors.

The agenda for our presentation is shown here. We will provide background on tazemetostat, our inhibitor of EZH2, then speak to the relevance of EZH2 to childhood tumors, and finally, we will outline our clinical development program in both adult and pediatric patients.

EZH2 is the catalytic subunit of the PRC2

chromatin remodeling complex. The SWI/SNF complex is another multimeric protein that is involved in chromatin remodeling and acts as an antagonist of PRC2.

Mutations in SWI/SNF components, notably INI1 or SMARCA4, interfere with normal SWI/SNF function, resulting in unopposed PRC2 activity. This then leads to hyper-repression of PRC2 target genes, potentiation of stem cell programs, and oncogenic transformation in affected cells.

Tumors with these SWI/SNF mutations, including malignant rhabdoid tumors or MRT, are characterized by their oncogenic dependence on H3K27 trimethylation.

Tazemetostat is a potent, selective, and orally bioavailable small molecule that is an inhibitor of the histone methyltransferase, EZH2. EZH2 itself is an enzyme that adds one, two, and ultimately three methyl groups unto histone H3 at the lysine 27 position.

H3K27 is considered a transcriptionally repressive mark. Since many of the target genes

under EZH2 regulation are tumor suppressors, excessive function of EZH2 is oncogenic in a number of cancers, including B-cell non-Hodgkin's lymphoma.

Now, this oncogenic drive can be reversed by pharmacologic inhibition of EZH2. Tazemetostat exhibits potent and long-lasting antitumor activity, both in in vitro and in vivo models of rhabdoid tumors characterized by INI1 loss or SMARCA4 loss.

Now, this includes malignant rhabdoid tumor of ovary, shown here on the right, which is also termed small cell carcinoma of ovary hypercalcemic type.

Rhabdoid tumors are among the most aggressive and lethal forms of human cancer. They're typically diagnosed in infants and children, but they can occur at any age, including in adults.

Malignant rhabdoid tumors share a common genetic feature and that is the complete loss of the protein INI1, also known as BAF1 or SMARCB1,

located on chromosome 22. More recently, lesions on chromosome 19, which result in loss of SMARCA4 protein, have also been found in rhabdoid tumors.

Detection of INI1 loss by immunohistochemistry is considered the diagnostic test for malignant rhabdoid tumors and as such, malignant rhabdoid tumors represent a group of uncommon tumors that can arise from any organ and tissues within the body but are most commonly found in brain, kidney, and other soft tissues.

When arising in the kidney, these tumors are termed rhabdoid tumor of the kidney, and these tumors have historically been treated on National Wilms Tumor Study Group and Intergroup Rhabdomyosarcoma Study protocols.

Even among uncommon childhood renal or soft tissue tumors, these cancers are rare. They're diagnosed most commonly in infants, and the prognosis is very poor, especially in the youngest of these infants.

When arising in the CNS, these tumors are terms atypical teratoid rhabdoid tumors. Again,

they're rare and most often diagnosed in infants, in which they tend to be infratentorial, as opposed to older children where they tend to have supratentorial tumors. As with rhabdoid tumors arising in other locations, the outcome of children with these tumors is dismal.

Now, the current treatment approach for rhabdoid tumors consist of multi-modality treatment. This includes maximal surgical resection and intensive multi-agent chemotherapy.

Radiotherapy may or may not be given, depending on the child's age. In the case of ATRT, autologous transplant and intrathecal chemotherapy are commonly used. However, as seen on this slide, both radiotherapy and intensive systematic chemotherapy all bring with them major morbidity and constraints to their delivery, especially in infants and young children.

Despite intensive multi-modality approaches taken, the survival outcomes for patients with rhabdoid tumors are extremely poor, regardless of the organ of origin for these tumors.

The median overall survival for ATRT, RTK, extra CNS, extra renal MRT is generally less than one year from initial diagnosis.

Tazemetostat initially entered into the clinic in 2013 in France in a first in-human phase 1 trial that involved patients with both B-cell non-Hodgkin's lymphoma and solid tumors.

The phase 2 portion of this study, which includes only NHL patients, started in a number of European and North American countries, as well as Australia in 2015 and 2016.

Our program in INI1-negative, and SMARCA4-negative tumors, and synovial sarcoma began just last year with the U.S. IND. The adult and pediatric studies were started approximately six months ago.

Since then, these studies have been expanded to countries in the European Union, Canada, Australia, and Taiwan. Tazemetostat was granted orphan drug designation for malignant rhabdoid tumors earlier this year.

Finally, we have an accepted IND for

mesothelioma patients who have a loss of function of the protein, BAP1, in the U.S., with our European submissions currently in progress.

The clinical trials experience in adults consists of the previously mentioned first in-human phase 1 study, which is now close to accrual. Our current active studies in adults include global phase 2 studies in B-cell non-Hodgkin's lymphoma, and the INI1-negative or SMARCA4-negative tumors, and synovial sarcoma.

The next slide summarizes the first in-human phase 1 experience in adults. The study is a standard 3-plus-3 dose escalation with expansion cohorts, as well as clinical pharmacology sub-studies for food effects and drug-drug interactions.

Tazemetostat was dosed orally from 100 milligrams to 1600 milligrams twice daily. The primary and secondary endpoints are standard for a phase 1 study of this type.

Although we observed promising clinical activity in lymphoma, as would be expected based on

the preclinical data, I will not review those data here today. Instead, I'll focus on the solid tumor experience.

Of the 37 solid tumor patients enrolled, we had 11 patients with tumors characterized by INI1 or SMARCA4 negativity, as shown here. As you can see, patients included those with malignant rhabdoid tumor, epithelioid sarcoma, malignant rhabdoid tumor of ovary, and thoracic sarcoma.

As you can see on this next slide, the aggregate safety experience among our phase 1 and phase 2 patients is quite favorable. The most common adverse events, regardless of attribution, were grade 1 and 2 asthenia, nausea, anorexia, constipation, dysgeusia, and emesis.

We also observed thrombocytopenia and neutropenia, which, in rare patients, can rise to grade 3 or 4 events in approximately 5 percent and 2 percent of patients, respectively.

However, this pattern of myelosuppression is unlikely that of more conventional cytotoxic chemotherapies in that the vast majority, 85 to

90 percent of patients, do not experience any myelosuppression while on study.

In this waterfall plot, which we presented at the European Cancer Congress in 2015, we can see that tumor reductions were selectively observed in adult patients with INI1-negative or SMARCA4-negative tumors.

No patient with any other solid tumor which did not have these genetic lesions experienced an objective response to tazemetostat.

This next slide details a 55-year-old male with an INI1-negative malignant rhabdoid tumor who was originally treated with definitive surgery and adjuvant radiotherapy. His response to initial therapy was short-lived, and he relapsed soon thereafter with bilateral cervical lymphadenopathy. After starting on tazemetostat, he showed loss of metabolic signal by PET after only four weeks.

By week 8, he had a radiographic complete response, and at week 20, he underwent re-biopsy of his lymph node, which confirmed a pathologically complete response.

When these data were presented in September 2015, the patient had been on study for 65 weeks in an ongoing complete response. This patient remains on study today, with no evidence of disease.

There are many lessons that we can learn from phase 1. For today's discussion, the most relevant findings are that adult patients with INI1-negative or SMARCA4-negative tumors experienced objective responses consisting of complete and partial response.

We've also observed patients with stable disease lasting six months or greater, which is of note given the aggressive nature of these tumors.

Our current pediatric phase 1 study of tazemetostat is outlined over the next several slides. It's currently open for accrual in the U.S., Denmark, France, the UK, Australia, with additional countries later to join.

All patients are required to have local testing showing INI1 or SMARCA4 negativity or the chromosomal translocation characteristic for synovial sarcoma. We are, however, collecting

archival tumor samples for central confirmatory immunohistochemistry and pathologic review.

The study uses a rolling-6 dose escalation design, and the starting dose of 240-milligram per metered squared twice a day was derived from physiologically-based pharmacokinetic modeling observed in adults using PK data that we obtained there.

Following dose escalation, we will enroll into expansion cohorts in each of the three categories of tumors shown here.

Shown on the next slide are the primary, secondary, and exploratory endpoints for the study. We will, after the dose escalation, to determine the phase 2 dose, the primary endpoint for the dose expansion phase of the study is overall response rate, with secondary endpoints being duration of response, PFS, overall survival, and safety.

The main inclusion criteria for the study are shown here, and you have the full set of inclusion criteria described in your briefing books. Patients must be age 6 months to 21 years,

and they must have relapsed or refractory disease.

Shown here are the main exclusion criteria, and again, the full exclusion criteria are described in your briefing books.

As of two weeks ago, we have enrolled 16 patients and are currently on the third dose cohort of 400-milligram per metered squared. As you can see, we have enrolled a number of rhabdoid tumor patients, along with patients having other INI1-negative tumors. The age range for our patients on study begins at 13 months and spans up to older teenagers.

We're currently using an oral suspension formulation of tazemetostat for our trial. It is prepared at the site's investigational pharmacy and provided to patients as a two-week supply. It can be swallowed or administered through a nasogastric or gastric tube. We're continuing with development of a commercial formulation for children that will be reconstituted in water.

In addition to our pediatric phase 1 study, we have additional ongoing studies to support

pediatric development. We're collaborating with the NCI in the pediatric preclinical testing program and the results from this collaboration were presented at the Molecular Targets meeting last fall.

In addition, we're in active discussions with the NCI to include tazemetostat in the pediatric MATCH trial that will be run by the Children's Oncology Group.

As others have highlighted, there are many challenges to developing novel agents for pediatric cancers. We feel that we've made substantial headway on two of the more common issues for sponsors, that of recruitment of children as patients and of having a pediatric formulation suitable for clinical trials.

However, we're still left with many challenges to consider. Malignant rhabdoid tumors are unquestionably rare, even in the pediatric population. To appropriately characterize safety, we plan to enroll up to 84 patients in our current phase 1 study with the final sample size to be

discussed with the agency when more clinical data are available. We will, however, supplement the safety database in children with our experience from adults across multiple tumor types.

As demonstrated, malignant rhabdoid tumors are uniformly aggressive tumors that are highly lethal in children. We propose that the current trial be considered as adequate and well-controlled to demonstrate safety and efficacy in this pediatric population and propose to have further discussions with the agency on this.

Finally, given the biology behind rhabdoid tumors, we propose that the common genetics underlying this disease, namely that of INI1 or SMARCA4 loss, be the distinguishing characteristic in defining the potential indication rather than using more traditional histology or organ of origin.

In summary, rhabdoid tumors are a rare disease with high unmet medical need. The safety profile of tazemetostat as monotherapy is favorable for development, both as a single agent and in

combination with other therapies.

Tazemetostat has shown promising clinical activity in patients with both B-cell non-Hodgkin's lymphoma, as well as solid tumors. We feel that study 102 may be appropriate for consideration of a written request.

Again, our thanks for this opportunity to present to the committee.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you very much. We will now take clarifying questions for the sponsor. Please remember that we have additional questions for the subcommittee, and this should be addressed exclusively to the sponsor.

Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter.

I put my name first, so then we'll do Julia, and then we'll do Nita, and then we'll do Peter. The couple of questions I had, the obvious one, have you done any PK documenting that this agent penetrates into the CNS?

DR. HO: Sure. In animal models, the drug does not penetrate in intact blood-brain barrier. However, of course, we do know that ATRT tumors are contrast-enhancing and may involve disruption of the blood-brain barrier.

Right now, it's unknown to us the extent to which tazemetostat crosses the blood-brain barrier in patients who have primary or metastatic brain tumors.

Now, in our pediatric study, we do plan to quantify tazemetostat in the CSF from subjects by collecting their CSF samples at certain times, if that is warranted, and to look at tazemetostat concentrations.

DR. PAPPO: A question regarding the adult use with BAP1 mutant tumors. Are you planning to expand this to melanoma and uveal melanoma syndrome with mesothelioma or just mesothelioma?

DR. HO: No, we're very interested in BAP1 mutations in uveal melanoma, in particular. We're starting off in mesothelioma, but that's certainly a direction that we would ultimately want to take.

DR. PAPPO: The final question is, are there already some combination chemotherapy trials with EZH2 inhibitor in adults that eventually could guide the combination therapies in pediatrics?

DR. HO: Absolutely. We've done, first off, preclinical work in NHL models. What we found is that the components of CHOP, commonly used in lymphomas, do have additivity or synergy with the drug. In particular, steroids are synergistic with the drug, but also alkylators as well.

We will be starting a study in adult patients with lymphoma of tazemetostat in combination with our CHOP. We are also going to be starting a combination study with a checkpoint inhibitor, actually, atezolizumab, which I understand the committee will hear a little bit more about later today.

DR. PAPPO: Thank you. Dr. Glade Bender?

DR. GLADE BENDER: Julia Glade Bender, Columbia University. I want to preface my remarks by saying that this is a very interesting agent for pediatrics. I noticed that there was no

preclinical toxicity data included in the preparation materials.

In particular, I wanted to know whether there was any cardiac toxicity, because those were inclusion-exclusion criteria. Also, these are going to be very young patients, potentially on for very long periods of time. Is there any long-term toxicity data in any animals? Finally, what happens if you stop the drug?

DR. HO: A series of questions. Let me make sure I take them all. If I miss one, just remind me.

With respect to cardiac toxicity, we've done, in adult animals, the standard four-week and three-month toxicology studies in rat and monkey. We've also done a juvenile rat study of three months' duration as well.

In none of those studies did we see any significant cardiac toxicity. Of course, you can imagine we're monitoring cardiac toxicity very closely in our adult studies, especially given the patient population and age. We haven't seen any

signals there, but, of course, it is still relatively early. So we need to follow that up some more.

The criteria that are described in the protocol are ones that are just fairly standard. They weren't placed there for any particular concern. Your other question?

DR. GLADE BENDER: Long-term toxicity.

DR. HO: In patients, we have patients from our phase 1 study that have been treated a year-and-a-half, two years, and even one patient coming up to two-and-a-half years. There hasn't been any evidence of any accumulative toxicities that have appeared over time.

The patients actually seem to be tolerating it well. When patients do have adverse events, actually, we tend to see them relatively early, and they don't become an issue.

DR. GLADE BENDER: But is there any data on developmental programs in juvenile animals?

DR. HO: No, we haven't started those studies, preclinical studies, as yet.

DR. GLADE BENDER: Has anybody stopped the drug who's responded to the drug, or what happens when you release the drug in the animal models?

DR. HO: That's a very good question. In the animal models, unlike some agents, if you stop the drug, the tumor doesn't always grow back. Of course, we only follow the animals through a defined period of time.

In our clinical trials, we do have long-term responders, both with malignant rhabdoid tumor and B-cell NHL. We have not stopped the drug on any of the patients.

Thankfully, the drug is orally bioavailable, so it's not like patients have to come back for infusions. Nevertheless, I think the question you raise is an excellent one, and that's something that we really have to work out on an individual basis with our investigators.

DR. PAPPO: Thank you. Dr. Seibel?

DR. SEIBEL: Peter, first of all, thank you, and we commend you for taking on this rare patient population that has a devastating outcome.

I have several questions. First of all, is there a time range for the response that you see or does it happen right away?

DR. HO: What we've seen in adults is that when there have been responses in the solid tumors, they actually have occurred, again, just from the phase 1 experience, with the first re-staging, scheduled re-staging at 8 weeks.

Now, that contrasts with our NHL experience, where we've seen that patients with B-cell disease have entered into an initial objective response anywhere from two months, again the first re-staging, all the way through 10 months.

There are patients with B-cell lymphomas who, in tracking their tumor measurements, have a slow, but persistent decline in their tumor load and eventually go into an initial response later.

We've also seen in the adult NHL population patients who have had an initial PR that anywhere from several months to even one year later convert from a PR to a CR. It's an interesting facet of the drug. In solid tumors, our experience is still

much more limited.

DR. SEIBEL: Do you have any data about resistance development?

DR. HO: We did do work in laboratory models. It's sort of a typical thing that my folks do, is incubate the tumor cells in increasing concentrations of the drug.

Initially, we actually had a difficult time generating resistance in mutant cells through this approach. Through persistence, we have those lines in place now, and we're continuing to characterize them.

DR. SEIBEL: You also commented on the unusual pattern for myelosuppression that you've seen in patients. Can you expand a bit more on that?

DR. SEIBEL: I think, certainly, we would say based on the phase 1 and phase 2 experience that thrombocytopenia and neutropenia can be drug-related.

We've seen some patients with lymphomas, later in their course on treatment as disease is

progressing, will experience thrombocytopenia and neutropenia that seems to be associated with disease progression and infiltration of the marrow.

However, we have also seen other patients who have seen that relatively early in a time course. Now, again, unlike a lot of drugs where there may be, I don't know, 15, 20 percent of patients have grade 3-4 neutropenia, but most of the other patients have some degree of lower grade myelosuppression. That's what we don't see.

Can I have the slide up, please? As you can see here, when we look at the degree of thrombocytopenia and neutropenia -- now, this comes from our phase 2 NHL studies, so just consider that.

What we've seen based on laboratory results is that, actually, grade 4 events are quite rare. There'll be patients who have some grade 3s, but overall, the incidence, as you can see here, of either a grade 3 or 4 neutropenia or thrombocytopenia is roughly 10 percent or less.

DR. SEIBEL: Then my last question is, are

there other molecular targets that may be available in the future that we could use for this drug or to identify patients who may respond to this drug?

DR. HO: Can I have the slide showing the SWI/SNF complex?

As alluded to earlier, the SWI/SNF complex is a very large multimeric protein. We've really only begun scratching the surface with respect to co-dependencies here.

We have looked at synovial sarcoma, because these tumors involve the translocation, which then ultimately affects the SS18 component of the complex that then results in reduced expression of INI1.

As you can see, there are many tumors here that are associated with other members of the SWI/SNF complex. At the same time, I wouldn't go so far to say that every single component of SWI/SNF and thus every tumor here represents a viable target.

I think there are things to consider, but certainly, I'm not sure that any single genetic

lesion in any one of these components may result in the same functional co-dependencies that we've seen in rhabdoid tumors, just continued work to be done.

DR. PAPPO: Thank you. Dr. Adamson?

DR. ADAMSON: I had a few questions, Peter, about dose. And I think for this drug, dose is going to be highly relevant, especially when we come to CNS tumors.

If I understand the adult data correctly -- and you can correct me -- you went up as high as 1600 milligram BID flat dosing, which means, by definition, 800 milligram BID flat dosing is no greater than 50 percent of the adult MTD and probably less than 50 percent of the adult MTD.

You started at a dose half of that at 240, which would be no greater than 25 percent of an MTD, which is an extraordinarily low dose for us historically.

You are, I would say, very painstakingly getting back up to a dose that is below the MTD. Can you clarify the rationale for this? Then I have a related question when we come down to

infants.

DR. HO: Fair enough. Can I have the slide for the dose selection for phase 2 in adults, please?

Indeed, we did not reach a more traditional definition which we all are comfortable with, meaning two or more DLTs and looking at the dose level below that as the MTD.

We did see one dose limiting toxicity of grade 4 thrombocytopenia in a patient at the highest dose level of the 1600 milligrams twice a day. That's 1 out of 6. But we did not get 2 out of 6. At that point, we looked across, as you can see here, efficacy, safety, and PKPD to derive the 800-milligram dose in adults as the recommended phase 2 dose.

You can see here that was based on efficacy in NHL where we had seen, with the smaller numbers in the phase 1 study, of course, that the efficacy was roughly similar between 800 and 1600. There were some increases in grade 3 or greater treatment-emergent adverse events between 800 and

1600.

Then lastly, let me speak to PKPD. What we did here was we looked at, as a PD marker, the inhibition of trimethylated H3K27, but we used skin as a surrogate tissue. When we evaluated that, you can see the dose response curve shown here, where there does seem to be a plateauing out at approximately 800 milligrams.

Again, to be fair, this is surrogate tissue. It may or may not reflect accurately what's in the tumor, but using all of these data, that's how we derived the dose.

Part of that rationale was that unlike a traditional cytotoxic drug, we feel that for the way that this drug works in terms of altering gene expression and then inducing an altered phenotype, that patients needed to be on it for chronic periods.

The question before from the committee, well, what would happen if you take a patient off, we don't know. We also did not want to necessarily push the dose to what would even be an MTD such

that patients might come off, so it was a consideration of that.

Now, we do have limited data from the adult phase 1 experience of H3K27 inhibition in tumor tissue.

If I could have that slide, please? I'll just show you what we have, and that is that in a couple of patients, oddly enough, INI1-negative patients, and these are adults, of course, rhabdoid tumors of kidney, shown above, epithelioid sarcoma below.

You can see on the left-most panel that for INI1 staining, there's a lot of blue cells, very little brown, showing INI1 negativity. There's still some brown staining and that results from stromal cells and infiltrating lymphocytes that do express INI1.

But that, at baseline, if one stains for H3K27 -- this is the middle panel -- you can see that in both tumors, all of the cells are diffusely positive, whereas by week 4, this was negative in 100 percent of all of the larger nucleated tumor

cells in the top panel and approximately half of the tumor cells in the lower panel.

It's limited data, but it does suggest some correlation certainly with what we're seeing in the skin. And in these cases, the reduction in the PD marker correlated with clinical activity in these patients.

We certainly need to have more data from the adults, both in NHL and in solid tumors. In the pediatric study, what we're trying to do is to look at H3K27 methylation in circulating the mononuclear cells instead of skin, understanding that it'll be difficult to get pre- and post-tumor biopsies.

DR. ADAMSON: Peter, let me drill that down a little more. Your recommended phase 2 dose in adults is the flat 800 based on PD.

DR. HO: Right.

DR. ADAMSON: I think the point I would make -- and this is not isolated here. When the recommended phase 2 dose in adults is well below the MTD, there's no reason to start below the recommended phase 2 dose when going in children.

By definition, you're at 50 percent or lower.

The reason that I think that's important, one is it impacts the efficiencies of these trials. You could have certainly begun, in my view, at your recommended phase 2 dose normalized. That would have put you, I think, close to dose level 4 of your study. That's water under the bridge, and that's okay. I think this applies to other drugs where we have to get out of the cytotoxic chemotherapy mode, but we always start below the adult MTD when we come to these drugs where we're not going in with the adult MTD.

DR. HO: Right.

DR. ADAMSON: The two related questions I have are, if you don't -- right now, you're stopping at 800, equivalent of 800 flat in the escalation scheme, I believe, right?

DR. HO: Sorry. The initial four dose levels chosen were based on PK modeling, but we'll actually be amending the study to include higher dose levels.

DR. ADAMSON: Okay. So I think, certainly,

if you don't see a signal in CNS, which may very much be a dose -- if it is going to occur with limited penetration, pushing in the CNS population, I think it would be incredibly important to do.

With that said, on the other end of the spectrum, as you work your way down into infants, where if you see efficacy, this could become highly relevant. As you know, that's where our knowledge of how they dosed drugs 50 years ago becomes even more limited.

Any consideration to flipping to a per kilo as a safety measure as you go below one year of age once you get to your recommended dose, if you see a signal, especially if we get into this 6-month range? It may not be in the relapsed setting, it may be in your next trial, to getting some experience with historical transitions to per kilo.

DR. HO: Absolutely. That's actually a question that we grappled with in designing the study, and I would say we're not necessarily wedded to body surface area-based dosing.

Certainly, in the younger children, we would

be open to using alternative parameters to decide the ultimate dose.

DR. PAPPO: Thank you. Dr. Warren?

DR. WARREN: Hey, Peter. I also want to echo the excitement around this drug.

I have a couple of questions that expand, once again, on Peter's. Does your preclinical testing inform at all about what target exposure you need for complete EZH2 inhibition? Is there a dose response so that higher doses are more, or do you hit a threshold at some point?

DR. HO: It depends on the model. In some models, there is a dose -- there's never no dose response, but in some cases, you do see a plateauing effect. Overall, there is a dose response such that higher doses can be better. Have we gone above that? It's not clear.

I think there are two components here. One certainly is dose as it should be, and the other is duration of therapy. One of the things that we see in preclinical models, which is a little different, for many screens, for small molecule anticancer

agents in vitro, it's a two-day or a three-day assay in vitro looking at cell kill.

We don't see effects generally in that case. We end up using 7- and 14-day incubations. Duration of exposure with drug is also an important parameter to go along with dose.

DR. WARREN: If you have a known target exposure preclinically, rather than using circulating PBMCs in your patients, is there some way to look at the concentration of the drug in the tumor to see if you're coming close?

DR. HO: That would be great. Just in the preclinical models, it's not clear that there is a single number in terms of target exposure. I'd want to be a little careful about extrapolating too much.

To your point about using intratumoral concentrations of drug to help decide the dose, I think we'd certainly be open to that. Always the practical issue is having a sample to analyze.

DR. WARREN: One last question. You know there's been some interest in evaluating this in

diffuse infiltrating midline tumors with the histo-mutation, which can also have effects on EZH2.

DR. HO: Right.

DR. WARREN: A recent study out of Europe showed that there was no cytotoxicity when you use this agent for that. Do you have any insight as to why that activity is lacking? Does that mean that the K27 biomarker that you're using may not be an appropriate biomarker?

DR. HO: It's difficult for me to comment on the recent findings there outside of our own clinical experience. For us, we have found that using H3K27 are the appropriate models, as they correlated what we're seeing in the clinic in terms of tumors that are sensitive in NHL and in the INI1. It does appear to be a very reasonable marker for us to use.

The issue always is translating that to tumor tissue in a clinical trial rather than a surrogate tissue.

DR. PAPPO: Thank you. Dr. DuBois?

DR. DuBOIS: Thank you, Peter.

A few questions. I'm not aware of EZH2 mutations in pediatrics, and I wonder if you've interrogated any commercial sequencing databases to see if these exist. If so, might that be an inclusion criterion to be considered perhaps in pediatric MATCH or other future trials?

DR. HO: Absolutely. I think that's a great question.

We have looked in various genetic databases. What we find is that in pediatric solid tumors, there certainly have been reports of EZH2 activating mutations in Ewing sarcoma.

In the other more common tumors in pediatrics that end up appearing in these databases, we really haven't fund much. Certainly, Ewing's would be something of interest and that's under consideration, essentially any pediatric tumor that has one of these known activating mutations for the pediatric MATCH study.

DR. DuBOIS: Then a subset of these children will have germline INI1 loss. And do you

anticipate any differential toxicity in that case or not really because they'll be heterozygotes?

DR. HO: That's a great question, too. We do allow for patients who have germline mutations into our current trial. Short of speculating, because I don't know what might be expected, I think that's just something that we're going to have to observe and analyze.

DR. DuBOIS: Last question. Can you update us on where things stand with the synovial sarcoma experience?

DR. HO: The phase 1 experience for synovial there, we did not see responses in those patients in phase 1.

Now, to be fair, as you know, it's a phase 1 study. Several of the patients were dosed at levels well below our recommended phase 2 dose. There was a patient who was treated at the recommended phase 2 dose that progressed very quickly, but then ends up being an N of 1.

We do have synovial sarcoma patients as part of the phase 2 study in adults. It's a separate

cohort entirely. Again, that's study started just a month before the pediatric study. It's been open for six months, so it's still accruing. We'll be looking closely at that for any lessons that we can learn for pediatric patients with synovial sarcoma.

DR. PAPPO: Thank you. Dr. Raetz?

DR. RAETZ: Thank you for your presentation. I have just two questions. I was wondering if you could expand on the rationale for 6 months being the lower age limit and whether there is any consideration for even studying younger infants?

DR. HO: Right. Also, another point that we had a lot of debate on in formulating the protocol. In this case, because for the pediatric study we are limiting ourselves to patients who have relapsed and refractory disease, we thought that basically even a very young patient diagnosed shortly after birth would have a certain amount of treatment, such that by the time they came on our study, they'd be 6 months.

Having said that, as we move forward, if we are seeing activity in children older than

6 months, we would certainly be open, with some caution, of course, to evaluating patients younger than 6 months.

DR. RAETZ: Just a second question. Would you anticipate any differences in the toxicity profile if it's administered after hydrotherapy in autologous transplants?

DR. HO: For that question, I think the answer is we do not anticipate differences. The reason why I say that is because in the adult experience, we did have many patients with NHL who came on study after an autologous transplant.

When we've looked at those patients, we don't see any gross differences in terms of the safety profile.

DR. PAPPO: Thank you. Dr. Weigel?

DR. WEIGEL: Thank you. I want to echo the appreciation for the presentation, Peter. This is very exciting.

I'm following along. And, actually, several of the things I was thinking follow along Peter Adamson and Katherine Warren's thoughts and trying

to understand optimizing the dose and dose exposure for the drug.

I wonder if you have any data to follow along their thoughts. If you think about -- I'll use the example of epithelioid sarcomas. It's a indolent, generally slow-creeping disease, and you compare that to a very aggressive malignant CNS rhabdoid in a small child.

They may have, biologically, similarities. I would argue they're actually very different tumors. If we're looking at biomarker targeting, what do we know about the dose exposure and the exposure levels needed between those types of tumors to say that we would be optimizing the dose, because it might be different for something like an epithelioid sarcoma, which is the example you used in the biomarker data that you have. How can we best ensure adequate dose exposure?

DR. HO: Again, I think that's an excellent question and one we have given a lot of thought to. Certainly, I accept that there may be differences depending on disease. Far from our phase 1

experience, we haven't seen that necessarily jump out in adults between solid tumors and lymphoma. That would be the first cut. Certainly, within the two examples that you mentioned, epithelioid sarcoma and MRT, it could very well be that there may be a need for different doses.

I think that's really something that we're looking at carefully in the pediatric study as we dose escalate. Again, I think it would be great if we can try to use patient-based tissue to see if there are, indeed, differences for us, especially in pediatrics where the difficulty is in having tumor tissue.

That's why we go to things such as circulating mononuclear cells and even looking at circulating DNA to see if that's informative to try to have some other tissue-based source for biomarker endpoints.

DR. WEIGEL: I think that sort of echoes my thought. I'm predicting we're going to need higher exposures for the tumors that we are most interested in treating. Therefore, underdosing in

the pediatric study, to me, would be the bigger concern, because I think then you, obviously, are going to treat the more indolent ones.

I think my bigger concern is coming in under what we would need for optimizing the drug.

DR. HO: Absolutely. Agreed.

DR. PAPPO: Thank you. Dr. MacDonald?

DR. MacDONALD: Tobey MacDonald, Emory. With regard to ATRT, are you going to pay any attention to the molecular subgrouping of the disease, specifically ASCL1-positive and negative status?

DR. HO: Right. Based on some of the recent literature and, indeed, even as a disease such as ATRT is becoming subdivided, certainly, we are collecting tissue to try to look at that.

I think you're referring to this recent publication. Certainly, within the groups of groupings of tumors that came out of this publication, we do see that one of the commonalities is SMARCB1 or in this INI1 deletions.

Beyond that, we are looking at where we can

at potential differences to see if the groups do respond differently. It's early, but we'll follow it.

DR. MacDONALD: Second question. In regard to CNS penetration in either preclinical or clinical, have you seen CNS disease response of any kind?

DR. HO: It's a mix. We've certainly had some patients, NHL patients, who had on study progression to CNS. We've also had one patient with a solid tumor from the phase 1 who did come in with a CNS metastasis. Actually, it was reported to us after the patient came on study. But that patient has had stable CNS disease over the course of something like 8 to 9 months or so. Maybe that's something there, maybe it's not. It's an N of 1. I think we're just going to have to look at this more.

In our formal phase 2 study of INI1 and SMARCA4-negative patients in adults, we are allowing on board patients who have asymptomatic CNS metastases, and so we can follow those patients

as well.

DR. MacDONALD: Final question. Just in our most young population with, again, CNS ATRT, in which radiation is a primary modality where parents and physicians would like to forego, any consideration of doing this as upfront drug in that particular patient population?

DR. HO: Absolutely. I think with diseases that are as devastating as these, it's really a lot of chemotherapy used up front. We would, certainly, if we are seeing the activity in the relapsed or refractory setting, be very open to moving it into the upfront setting in combination.

DR. MacDONALD: Thank you.

DR. PAPPO: Ms. Haylock?

MS. HAYLOCK: I hesitate to even bring this up and it's not really a question, but it's just a comment.

In the lay literature and also in the scientific literature, there's an increased presence of an interest in the impact of sugars on cancer cells to the point where patients are

oftentimes now refusing to take contrast mediums and things like that just because of the high amount of sugar.

I just looked up the formulation of Ora-Sweet, your medium, and it does contain sucrose, glycerin, and sorbitol as an oral syrup. If you divide that up or do the math in terms of the dose, patients will be taking quite a bit of sugar.

I'm just commenting, I guess, that there is a possibility that some patients, families might be questioning the impact of significant amounts of sugar in this drug.

DR. HO: That's a very fair comment. In the current formulation, which is just in Ora-Sweet, it is sweet. We've tested it, and we tasted it. We would like to develop the later-stage formulation that starts moving away from that. We agree.

DR. PAPPO: Thank you. I had another question. Is there any data on all the other tumors that are included that are INI1-negative, whether they have a common pathway of

overexpression of EZH2 and trimethylation of K327, for example, myoepithelial carcinoma, epithelioid sarcoma, medullary renal carcinoma, or is it just a representation of the tumor, but it's not a really a driver? Has anybody looked at those tumors and document that they overexpress EZH2 or not?

DR. HO: In terms of driver mutations, one of the commonalities for many of these tumors is that when there is, let's say, an INI1 loss or a SMARCA4 loss, these tumors don't have many other mutations. It's not definitive, but it would certainly point to the fact that they're playing more than just a passenger role. There has been data that has come out for certainly renal medullary carcinoma that there have been many other mutations identified.

We're starting to look at that where we can. Of course, a lot of the models where one might be doing this are hard to find in some of these rare tumors.

DR. PAPPO: Thank you. Any additional questions? Steve?

DR. DuBOIS: Peter, your slide reminded me about the role of CDK46 in rhabdoid tumors, and I wondered if you or anyone, to your knowledge, is looking at the combination of tazemetostat and a CDK46 inhibitor in preclinical models?

DR. HO: That's a great question. We have not ourselves there, but certainly something to think about. There are some other EZH2 inhibitors either in the clinic or preclinically. I don't know what people might've done with CDK46s.

DR. PAPPO: Thank you. Any additional questions?

(No response.)

DR. PAPPO: We have plenty of time.

(Laughter.)

DR. PAPPO: Thank you very much.

DR. HO: Thank you.

DR. PAPPO: I'm going to speak very slowly like Dory.

(Laughter.)

Questions to the Subcommittee and Discussion

DR. PAPPO: There are no OPH speakers. We

will now proceed with the questions to the committee and panel discussions.

I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Let's start with the first question.

DR. BARONE: First question, please consider the relevant pediatric cancers, including non-Hodgkin's lymphoma, for which a biologic rationale for the evaluation of tazemetostat exists.

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

DR. DuBOIS: We haven't really talked about the neuroblastoma. I'll just point out for the record that Kim Stegmaier presented a plenary talk at the most recent ANR meeting earlier this month showing very nice preclinical data for EZH2 inhibition in neuroblastoma. I would encourage the sponsor to consider neuroblastoma as a potential

indication.

DR. PAPPO: Thank you. Dr. Warren?

DR. WARREN: I think there's interest in pursuing this for CNS tumors, but given the poor CNS penetration, I think we should investigate alternate methods of delivery to the CNS.

DR. PAPPO: Thank you? Any additional -- yes, Dr. Brown?

DR. BROWN: Pat Brown. Just to comment on a non-Hodgkin's lymphoma, since that's specifically listed, I think it's very smart not to try to address that with the first studies.

I think there may be very rare pediatric patients that have EZH2 mutant non-Hodgkin's lymphoma, but it's going to be extremely rare. I think down the line, that may be a subset that can be included in small efficacy studies, but I think it's appropriate not to include that in the earliest studies.

DR. PAPPO: Thank you. Any additional questions or suggestions?

(No response.)

DR. PAPPO: I'm going to try to sum this up. There appears to be some promising preclinical data using EZH2 inhibitors in neuroblastoma, so we encourage you to consider this subset of patients for inclusion in your trial.

Also, given the potentially low penetration of this agent into the CNS, consider alternative methods for delivery of this drug in patients with CNS tumors.

Finally, down the line, try to include small efficacy studies on some patients that have EZH2 mutations, but at this stage, not including NHL is a good idea. Anything else?

(No response.)

DR. PAPPO: We will now move to the second question.

DR. BARONE: Please comment on trial design considered to be adequate and well controlled in order to demonstrate efficacy and safety in this pediatric population given the rarity of the disease.

DR. PAPPO: Thank you very much. If there

are no questions or comments concerning the wording or the question, we will now open the question for discussion.

There were a few comments on trial design, so if anybody wants to mention something.

Julia?

DR. GLADE BENDER: I think the current trial design, given the rarity of disease, again, if we see significant activity, would be pretty compelling evidence.

I wanted to suggest that the rhabdoid tumors that present in very early childhood are very aggressive, and they are faced with a prognosis that you put up which is less than 20 percent. They progress rapidly.

The ones that we generally can cure are the ones that are resectable. I would suggest that another way for you to get your tumor penetration data is to allow a very short window of drug in newly-diagnosed patients and then have them go to resection.

I think we would learn a lot that way, and

the one could decide whether or not the drug should be continued after that.

DR. PAPPO: Thank you very much. I just wanted to ask Dr. Pazdur to introduce himself.

MR. PAZDUR: Richard Pazdur, Office of Hematology and Oncology Products.

DR. PAPPO: Thank you very much.

Any additional comments regarding this question? Yes?

DR. WEIGEL: I think just to echo what's been said, we would encourage dose optimization and escalation, as it sounds like you're planning, on a current amendment and encourage inclusion potentially of infants to really optimize use of the drug in the target populations.

DR. PAPPO: Thank you. Dr. Adamson?

DR. ADAMSON: Again, I think in a very rare disease, if there's a robust single-agent response rate, that would be welcome news and, I think, would likely meet the goals of bringing effective therapy to an unmet need.

To echo some of the comments, when it comes

to CNS, I would hate to dismiss this agent because we didn't get to an exposure that's associated with activity.

My concern right now is that we're taking a sluggish approach to dose escalation. If there's safety data going up to 1600 BID, we're a far way away from that.

CNS penetration -- and I agree, Peter, with your statement earlier, this is not an intact blood-brain barrier, but nonetheless, I think we may have to push the dose in the CNS cohort before I would be confident that we're not seeing a signal there.

I wouldn't necessarily dismiss this agent in 20 patients at a generalized solid tumor dose if we haven't really pushed the dose in that subset of children.

DR. PAPPO: Thank you. Dr. Reaman?

DR. REAMAN: I had the same concern about the dose and the CNS penetration. When you were mentioning before that it doesn't appear that this crosses an intact blood-brain barrier, were there

dose effects? With higher dose, would you expect to see more of this drug reach the brain through an intact or not intact blood-brain barrier?

DR. HO: [Inaudible - off mic] -- regard as yet. The preclinical studies that were done were at a single dose, typical biodistribution.

DR. REAMAN: A relatively low dose, the single?

DR. HO: It was a modest dose, but certainly that's something that we can continue looking at.

DR. PAPPO: Thank you very much. Dr. MacDonald?

DR. MacDONALD: This may be piling on. In that infant ATRT population, in terms of giving drug exposure, then resection, followed by a better understanding of the CNS penetration, we have patients who, when given the options of treatment, have declined all treatment. There's definitely a patient population out there that could undergo that.

DR. PAPPO: Thank you. Any additional questions?

DR. ARMSTRONG: I'm not sure if it's conveniently in this question, but we actually haven't brought up the issue of your biomarker, what you're using, and how well that's established. I just would say it may fit it in here as well, which is to make sure that if you're really looking at these negative tumors, that you've done a good job of correlating if it's IHC with other measures of the INI1 in the tumors or the lack of INI1.

DR. PAPPO: Thank you for that comment. Any comments about that?

DR. GLADE BENDER: Just to echo what everybody said about dose escalation, if your dose-limiting toxicity was grade 4 thrombocytopenia, I'm not even sure it would meet our definition of a dose-limiting toxicity.

Therefore, I really think that escalating beyond that dose is reasonable. We manage thrombocytopenia all the time, and I promise you, any other therapy that they might get other than this would certainly cause grade 4 thrombocytopenia.

DR. PAPPO: Thank you very much. Any addition comments or suggestions?

(No response.)

DR. PAPPO: A recurring theme has been to try to optimize exposure and to reconsider the dose escalation. Apparently, you start relatively low; also, to encourage dose optimization and inclusion of infants to optimize your clinical findings in phase 1 studies.

In addition to that, there has been a recurring theme of the concern of CNS penetration of this drug, and it is unclear whether increasing the dose will overcome the problems that we'd have with the blood-brain barrier.

Perhaps an alternative design of a study would be to give the drug initially, potentially resectable tumor, and then obtain tissue and try to measure drug. That could also serve as a surrogate for a biomarker and identification to be sure that you're doing what you're doing with the trimethylation of K327.

I believe that's about it. I don't know if

you had any other comments or suggestions.

(No response.)

DR. PAPPO: We will move now question number 3.

DR. BARONE: Please consider the necessity for an international collaborative study given the very rare cancers for which this drug might prove relevant.

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

DR. ADAMSON: Again, I would commend the company for already embarking on an international approach for this disease.

Certainly, we would all view a positive phase 2 will be extremely welcomed, but we'd know that would be the beginning of the drug development plan. And as we were to move into especially MRT, where cytotoxic therapy I think has a relatively established role to -- at least some extent, it will require international collaboration as we move

this into -- should it be a positive phase 2 if we were to move this into front line. In this rare population, I anticipate international collaboration is going to be required, and I think would be welcome.

DR. PAPPO: I agree with you, and I think that some of the statistics that were provided in the background of the protocol are a little bit overinflated. I don't know if they were from CDER or what.

You were quoting about 450 patients. That sounds like a little bit too much. I don't know if it was just related to the rhabdoid tumors or it was all INI1-negative tumors. For rhabdoids, if you look at brain subtissue and kidney, it would be probably not more than a 100 and 150 patients a year. I think it will be necessary to do an internationally collaborative study in specific subsets of patients if this drug appears to be very promising.

Dr. Reaman, did you have -- or anybody else have a --

DR. REAMAN: We would certainly encourage the international collaboration. I think it's definitely the way to go after a promising phase 2 study.

DR. PAPPO: To wrap this up, you need to be commended for already starting an international collaborative trial on the phase 1 study. If there appears to be a signal of activity in a specific subset, it will be necessary to conduct an international study to answer the question of activity. Anything else?

(No response.)

DR. PAPPO: We will now move to question number 4.

DR. BARONE: Please comment on any safety concerns relating to the use of tazemetostat in pediatric patients. In addition, please comment on combining safety data across multiple mutation types.

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

Dr. Brown?

DR. BROWN: Pat Brown. I would just think that trying to differentiate where possible safety patterns in patients with germline versus acquired would probably be the most relevant.

I don't think within acquired mutations, safety patterns across multiple mutation types are likely to differ, but certainly germline versus acquired could differ substantially and should be addressed to the extent possible.

DR. PAPPO: Thank you. Yes, Julie?

DR. GLADE BENDER: Julia Glade Bender, again.

To build on Pat Brown's comment, I wonder, given that strange sporadic myelosuppression that you see, whether there's something in the germline, a host factor, that might explain that as well.

My comments earlier regarding toxicity, I think if you're treating very young patients, and you're expecting to treat them long-term, because we don't know if you can stop a small molecule inhibitor of the pathway that it would be important

to build in growth development and endocrine outcomes early on just to be able to have that data which will be very important in the future, just a few assessments.

Finally, I would say that given that it's a very rare population, I would limit the inclusion-exclusion criteria to things that are really vital because we've all had patients whose QTc is one or two points above the cutoff or a little bit below on the ejection fraction.

We would love to be able to enroll those patients. There isn't really a signal for cardiotoxicity. I might remove that from the inclusion-exclusion criteria.

DR. PAPPO: Excellent point. Any additional questions or comments? Yes, Dr. Warren?

DR. WARREN: This is a minor comment, but I think some attention should be paid to see if there's any difference in safety or tolerability in patients who are on steroids and those who are not. I'm not sure it necessitates the different cohort, but at least some attention.

DR. PAPPO: Thank you.

Any addition comments or questions? Yes?

DR. NEVILLE: Just to hammer the dose optimization, I think you won't be able to tell everything about safety until you get to the appropriate dose.

DR. PAPPO: Thank you. Any additional comments?

(No response.)

DR. PAPPO: We believe that it will be important to identify the safety patterns in patients that have a germline mutation versus those who do not have a germline mutation; also take into consideration host factors in young patients; and, try to incorporate into your studies, after you identify the dose in phase 1, patients that include long-term follow-up of growth and endocrine development.

Also, try to limit your inclusion-exclusion criteria for minor things such as the QTc; and, finally, to identify toxicities in patients that are on steroids and those who are not receiving

steroids. Anything else?

(No response.)

DR. PAPPO: Question number 5.

DR. BARONE: Please comment on the adequacy of the current pediatric formulation and any future plans.

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

Dr. Adamson?

DR. ADAMSON: Again, I commend the company for developing a liquid formulation that could begin these studies. I don't know about the solubility of this drug, but it invariably is a challenge.

I think with efficacy, I would imagine there will have to be further development before a commercialization could take place, but I don't know that for a fact.

What I did note, I think at least one of the studies, you did a bioavailability study with an intravenous formulation, unless I'm not remembering

that correctly, or was that just an animal study?

DR. HO: Animal.

DR. ADAMSON: Just animal, okay. It gets back to one of the questions that I did have earlier. As you began to see a plateau in the pharmacodynamic effect, have you seen saturation in bioavailability?

It sounded like it was linear up to 1600, but I don't know if there are preclinical concerns about that. If there were, that might impact how one approaches this dosing-wise and schedule-wise, if it's, in fact, saturable.

DR. HO: Right. In the adult experience, we had linear PK through the 1600 milligram. We certainly didn't see any plateauing or saturability there.

DR. PAPPO: Dr. Brown?

DR. BROWN: One question. I apologize if you addressed it. It was about nasogastric or gastrostomy tube feeding. Has the drug been tested as to whether it can be used in that setting?

DR. HO: It has.

DR. BROWN: It has. Good.

DR. PAPPO: Any additional questions or comments?

(No response.)

DR. PAPPO: There were not a whole lot of issues regarding this question. Again, the company needs to be commended for developing a liquid formulation. And if this moves forward, there has to be further development of this oral formulation.

There was a question about saturation and bioavailability, and, apparently, this has been addressed in the adult study up to a dose of 1600 BID.

The question about NG and G tube feedings has also been answered by the company.

Dr. Reaman?

DR. REAMAN: Less sugar. Less sugar.

Adjournment

DR. PAPPO: That's right. Yes, less sugar. Sorry.

I think we're done with the questions. At this time, I'm good. I'm not skipping anybody.

We will now break for lunch. It will be in Room 1504. We will reconvene in this room at 1:20.

Panel members, please remember there should be no discussion of the meeting topic during lunch amongst yourselves or with any other members of the audience. Thank you very much.

(Whereupon, at 11:08 a.m., the morning session was adjourned.)