FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

(pedsODAC)

Thursday, June 18, 2020

1:21 p.m. to 3:05 p.m.

Topic 2

Afternoon Session

Virtual Meeting

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C O N T E N T S

P R O C E E D I N G S

(1:21 p.m.)

Call to Order

Introduction of Committee

DR. PAPPO: Good afternoon and welcome to the final session of the Pediatric ODAC meeting. For media and press, I would like to announce the FDA press contact is Nathan Arnold, and his email is nathan.arnold@fda.hhs.gov, and his phone number is 301-796-6248.

My name is Alberto Pappo, and I will be chairing today's virtual meeting. I will now call the afternoon session of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee to order.

We will proceed with introducing our panel members again, and as we've done in previous sessions, we will use a call/respond method in which I will call the name of the panelist, and then you will introduce yourself for the record. We will start with David Mitchell.

MR. MITCHELL: Thank you. I'm sorry,

Doctor. I'm David Mitchell. I'm the consumer representative. I'm also a cancer patient with multiple myeloma.

DR. PAPPO: My name is Alberto Pappo. I'm a pediatric oncologist at St. Jude Children's Research Hospital, and I'm the chairperson for the Pediatric ODAC meeting.

Dr. Cheng?

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

DR. PAPPO: Dr. Catherine Bollard?

DR. BOLLARD: Hi. I'm Dr. Catherine Bollard from George Washington University and Children's National in Washington, DC.

DR. PAPPO: Dr. Steven DuBois?

DR. DuBOIS: Steve DuBois, Dana-Farber Boston Children's. I'm a pediatric oncologist.

DR. PAPPO: Dr. Ira Dunkel?

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

DR. PAPPO: Dr. Julia Glade Bender?

DR. GLADE BENDER: Good afternoon. I'm Julia Glade Bender also from Memorial Sloan Kettering in New York City, and I'm a pediatric oncologist.

DR. PAPPO: Dr. Richard Gorlick?

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

DR. PAPPO: Dr. Theodore Laetsch?

DR. LAETSCH: Hi. I'm Ted Laetsch, a pediatric oncologist at UT Southwestern in Dallas.

DR. PAPPO: Donna Ludwinski?

MS. LUDWINSKI: Hi. I'm Donna Ludwinski, a patient representative with Solving Kid's Cancer in New York.

DR. PAPPO: Dr. Andy Kolb?

DR. KOLB: Yes. Hi. This is Andy Kolb. I'm a pediatric oncologist and director of the Nemours Center for Cancer and Blood Disorders in Wilmington, Delaware.

DR. PAPPO: Dr. Katherine Janeway?

DR. JANEWAY: Hi. This is Katherine

Janeway or Katie Janeway. I am a pediatric oncologist at Dana-Farber and Boston Children's Hospital in Boston, Massachusetts.

DR. PAPPO: Dr. Naynesh Kamani?

DR. KAMANI: Hi. Good afternoon. This is Naynesh Kamani. I'm a pediatric immunologist bone marrow transplanter from Children's National in Washington, DC.

DR. PAPPO: Dr. Tobey MacDonald?

DR. MacDONALD: Hi. I'm Tobey MacDonald, pediatric neuro-oncologist at Emory University and Children's Healthcare of Atlanta.

DR. PAPPO: Dr. Leo Mascarenhas?

DR. MASCARENHAS: Hi. I'm Leo Mascarenhas. I'm the deputy director for the Cancer and Blood Disease Institute and head of oncology at Children's Hospital Los Angeles, The University of Southern California.

DR. PAPPO: Dr. William Parsons?

DR. PARSONS: Will Parsons, a pediatric oncologist at Texas Children's Hospital and Baylor College of Medicine in Houston, Texas.

DR. PAPPO: Dr. Elizabeth Raetz?

DR. RAETZ: Hi. I'm Elizabeth Raetz, a pediatric oncologist at New York University.

DR. PAPPO: Dr. Nita Seibel?

DR. SEIBEL: Hi. Good afternoon. I'm Nita Seibel, a pediatric oncologist and the clinical investigator at the Cancer Institute,

DR. PAPPO: Dr. Malcolm Smith?

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

DR. PAPPO: Dr. LaToya Bonner?

CDR BONNER: Hi. LaToya Bonner, DFO for this meeting.

DR. PAPPO: Dr. Gregory Reaman?

DR. REAMAN: Hi. Good afternoon. Greg Reaman. I'm associate director for pediatric oncology in the FDA's Oncology Center of Excellence.

DR. PAPPO: And Dr. Denise Casey?

DR. CASEY: Hi. This is Denise Casey,

pediatric oncologist, FDA, Division of Oncology 3.

DR. PAPPO: Dr. Leslie Doros?

DR. DOROS: Hi. This is Leslie Doros, FDA, Division of Oncology 3, pediatric oncologist.

DR. PAPPO: And Dr. Megan Zimmerman?

DR. ZIMMERMAN: Hi. Megan Zimmerman. I'm a pediatric oncologist and clinical reviewer at FDA.

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

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

Conflict of Interest Statement

CDR BONNER: Thank you.

The Food and Drug Administration is convening today's meeting of the Pediatric Oncology Subcommittee of the Oncologic Drug Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members of the committee and temporary voting members of the subcommittee are special government employees or regular federal employees from other

agencies and are subject to federal conflict of interest laws and regulations.

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

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

Related to the discussion of today's meeting, members of the committee and temporary voting members of the subcommittee 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.

For today's agenda, information will be presented regarding pediatric development plans for two products that are in development for an oncology indication. The subcommittee will consider and discuss issues relating to the development of each product for pediatric use and provide guidance to facilitate the formulation of written requests for pediatric studies if appropriate. The product under consideration for the assessment is SNDX-5613, presentation by Syndax

Pharmaceuticals, Incorporated.

This is a particular matters meeting during which specific matters related to SNDX-5613 will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Drs. Ira Dunkel and Theodore Laetsch.

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

Dr. Laetsch's waiver involves nine of his employer's research contracts. The contracts are for various studies funded by Onyx Pharmaceuticals, Children's Hospital of Los Angeles, Novartis, Janssen Research and Development, AbbVie, and a potentially competing firm. In addition, his employer is in negotiation for two research contracts with potentially competing firms.

The waivers allow these individuals to participate fully in today's deliberation. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/advisorycommittees/committeesmeetingmaterials/drugs/default.htm. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have made concerning the product at issue.

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

employed by Merck & Company.

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

DR. PAPPO: Thank you very much.

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

For this reason, the FDA encourages all participants, including the applicant's

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

Likewise, 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 presenting.

We will now proceed with Syndax Pharmaceuticals' presentation.

Industry Presentation - Michael Meyers

DR. MEYERS: Good afternoon. I'm Michael Myers, chief medical officer at Syndax. We want to thank Dr. Reaman, the FDA, and the ODAC for inviting us to discuss the pediatric development of SNDX-5613. Given the poor prognosis for children with MLL-r leukemia, development of targeted agents

should be rapid and efficient as we endeavor to provide durable benefits to this severely underserved patient population.

At the ACCELERATE meeting in January, regulators and the pediatric oncology community shared our enthusiasm in developing SNDX-5613. We've also had discussions with the FDA and the EMA, and they are urging us to rapidly evaluate this promising treatment in children.

SNDX-5613, or more simply 5613, is a potent, highly selective, oral menin-MLL1 inhibitor that has robust therapeutic potential for patients with MLL-rearranged leukemias. Menin is a chromatin associated scaffold protein that mediates transcriptional regulation but has no known enzymatic activity. Its MLL1 binding pockets, highlighted here, is discrete and quite amenable to small-molecule drug design, as you can see with one of our inhibitors bound at this site.

5613 binds to menin with high affinity, inhibiting binding of both MLL1 fusion and wild-type MLL1 proteins. It displays

antiproliferative activity across a range of cells harboring different MLL-r fusions.

Today I will discuss the urgent unmet need for new therapeutic approaches for children with MLL-r leukemias, then I will describe the compelling rationale for developing 5613 and share supporting nonclinical and early clinical data, and most importantly, I'll present our perspective on the pediatric clinical development program.

Rearrangement of the MLL gene is the transforming event, an oncogenic driver in 5 to 10 percent of acute leukemias in both adults and children. In infant ALL, it's especially prevalent, appearing in up to 70 percent of cases. MLL-r leukemia is aggressive, resistant to therapy, and has a high frequency of early relapse. MLL rearrangement is a powerful negative prognostic factor with dismal five-year, event-free, and overall survival compared to unselected patients, therefore, new therapeutic approaches are needed urgently.

Now, let's turn to our justification

for the development of menin inhibitors, specifically 5613. Spontaneous translocations involving the MLL1 locus create oncogenic MLL fusion proteins. These fusion proteins bind to menin, resulting in transcriptional dysregulation of target genes such as HOX-A and NIS1. This in turn leads to the initiation and maintenance of the leukemic state.

Shown here, menin inhibitors specifically block the Binding of MLL fusion proteins to menin, causing its dissociation from chromatin and downregulation of expression of the critical target genes. This leads to terminal differentiation of leukemic cells and cell death.

In vitro and in vivo data demonstrate the therapeutic potential of agents that inhibit the interaction between MLL1 and menin. Using a prototypic inhibitor, we showed that single-agent menin inhibition produces deep and durable responses and profound survival benefit in patient-derived xenograft models of MLL-r pediatric ALLs.

Among 8 MLL-r PDXs covering 5 different fusions, 7 had a highly significant survival benefit after only 28 days of treatment. The vehicle control's not shown here. A T1011 MLL-r PDX and the negative control PDX that did not contain an MLL rearrangement did not respond. Two models had profound responses with many mice surviving beyond one year. In these animals, no human CD45-positive cells could be found in any compartment at sacrifice.

5613, our clinical candidate, has a Ki of approximately 149 picomolar. It has potent antiproliferative activity against multiple cell lines with an IC50 of approximately 10 to 20 nanomolar and a plasma IC50 of approximately 50 nanomolar. Like many drugs, 5613 is metabolized by CYP3A4, but it does not inhibit or induce cytochrome P450 enzymes. The hERG IC50 is in the 5 to 15 micromolar range, so close cardiac monitoring is included in our phase 1 trials.

To investigate the potential less activity of 5613, we used the disseminated MOLM-13 xenograft

model. This is a very aggressive MLL-r model that may serve as an analog of the difficult-to-treat leukemia. Here, engrafted mice were randomized to receive either control chow or chow containing multiple dose strengths of 5613 for 28 days. All doses of 5613 showed significant survival benefit versus controls, but there was no discrimination among the three highest dose groups.

Analysis of human CD45-positive burden on day 33 revealed a more defined dose-response relationship. Only the two highest doses demonstrated marked reductions in CD45-positive cells and there was no difference between these two doses suggesting a maximal response.

To predict the plasma exposures likely to be needed for leukemic control in humans, we examined 5613 steady-state levels over 24 hours in mice. The graph on the right shows that only the two doses that achieved marked decreases in human CD45-positive cells were associated with plasma concentrations of 5613 that remained above the projected IC95 for most of the 24-hour period. The

drug exposures achieved for the lower of these two doses have been adopted as PK targets in our adult phase 1 trial.

Twenty-eight day oral toxicology studies were conducted in rats and dogs. Target organs identified were the heart with ECG changes in dog; eyes with cataracts in rats; bone marrow; liver; lymphoid tissues; and endocrine and reproductive system. The dose-limiting toxicity was weight loss/appetite suppression observed in the dog, and this was used to establish the highest non-severely toxic dose for calculating the starting dose for our first-in-human trial.

AUGMENT-101 is our ongoing phase 1/2 trial designed to identify maximum tolerated doses and recommended phase 2 doses of 5613 in adults with relapsed or refractory acute leukemia, and is agnostic of genomic abnormality. Because 5613 is metabolized by CYP3A4, and patients on potent CYP3A4 inhibitors may have increased exposures, the study has two arms. Arm A includes patients not on the strong CYP3A4 inhibitor and arm B includes

patients who are on the strong CYP3A4 inhibitor.

The phase 2 expansion will explore the safety and efficacy of 5613 dosed at RP2D in three cohorts, MLL-r ALL, MLL1 AML, and NPM1c AML.

Five of six patients reported at least one treatment-related adverse event. Consistent with the nonclinical findings, grade 1 or 2 QTc prolongations were observed but were asymptomatic and resolved spontaneously or following dose interruption or reduction. None of the treatment-related events were greater than or equal to grade 3 or assessed as serious.

Here is a summary of the patients treated on arm B, those on a strong CYP3A4 inhibitor. A 69 year old had an MLL rearrangement. She was dosed at 226 milligrams q12 hours and achieved drug exposures predicted to be necessary for clinical activity. Indeed, she achieved the CRi by day 28, which subsequently improved to a CR.

Here, we also see patients treated on arm A. The 32 year old had an MLL rearrangement but did not achieve the target plasma exposures.

As expected, this patient's disease did not respond to therapy.

As of April 30th, 6 children with MLL-r leukemias between 17 months and 10 years old have been treated under compassionate-use protocols. None were receiving CYP3A4 inhibitors. The children received a range of doses up to the equivalent of adult dose level 3. Notably, four of the children required interruptions of 5613 to receive aggressive cytotoxic chemotherapy to control rapidly progressive disease.

Given the nature of compassionate use, limited safety and PK data are available. All the children have tolerated therapy, two had treatment-related grade 3 adverse events of nausea and vomiting that responded to standard antiemetics, and no child experienced a QTc prolongation. As of the cutoff date, no responses have been noted but no child had exhibited sustained PK exposures predicted as necessary for efficacy.

Based on AUCs adjusted for dose and body

surface area, the children treated in the compassionate-use program and the adult patients in arm A appeared to have similar exposures to 5613. We believe that safety data will also be comparable at equivalent exposures, and we propose starting the phase 1 pediatric trial at the highest dose level with an acceptable safety profile in our phase 1 adult trial or in the compassionate-use pediatric patients.

We have seen in the phase 1 trial that adequate exposures can be achieved in adults, and we believe that with continued dose escalation and prolonged dosing, we can achieve and sustain the target exposures likely to result in clinical benefit in children.

Finally, I'd like to discuss our pediatric development program and present our position that, based on the data we've presented today, clinical development of 5613 in pediatric MLL-r leukemias should be responsibly accelerated so that children with this rare disease can have access to this promising drug in a clinical trial.

It's clear from conversations with leading pediatric oncologists and our experience in the compassionate-use program that we should focus our development of 5613 in combination with established chemotherapy backbones. Because of the aggressive nature of the disease, a clinical trial should allow for investigation of targeted drugs such as 5613 as monotherapy and also in combination with chemotherapy regimens that have been the backbone of treatment for pediatric acute leukemias.

Because it is unlikely that 5613 will initially replace chemotherapy, our plan in phase 2 is to treat children by adding 5613 to well-established chemotherapy regimens. We're still in the early stages of planning our phase 2 trial but recognize the importance of a trial design that isolates the effects of 5613 versus chemotherapy. An example of such a trial is shown here on the bottom.

We also recognize that infant ALL may require a different study design. Our intention is to collaborate with the FDA and COG to align on the

phase 2 strategy. Thus, our phase 1 study was designed to investigate the PK, safety, MTD, and RP2D of 5613 in children both as monotherapy and in combination with chemotherapy. We believe that our proposed trial design will efficiently provide this information.

Our phase 1 trial will enroll children who have refractory or relapsed acute leukemia with MLL-r or NPM1c mutations. The definitions of refractory and relapsed leukemia are specific for myeloid versus lymphoid disease and are consistent with COG guidance. Children from 1 month to 21 years of age will be included. These children will have no available effective therapeutic options.

Children will take 5613 orally every 12 hours as monotherapy for up to 84 days. Prior to enrollment and during treatment, use of typical cytoreduction regimens to control white blood cell counts is allowed.

Dose-limiting toxicity will be assessed over the first 28 days of monotherapy. Children will be assigned sequentially to escalating dose

levels, and dose escalation decisions will be based on the modified continual reassessment model with two patients per cohort to expose fewer children to subtherapeutic doses and to collect more data around the recommended phase 2 dose.

However, if children have rapid progression after at least 7 days of monotherapy, they may transition to combination therapy with 5613 and predefined standard salvage chemotherapy. The purpose of the chemotherapy is not to achieve remission but rather to provide more aggressive control of leukemic burden while allowing continued dosing of 5613. If children transition to combination therapy prior to day 28, a new DLC assessment window will begin and will last 28 days.

Initially, there will be no dose adjustments when transitioning to combination therapy, however, based on the observed toxicities during the combination regimen, dose escalations in the monotherapy regimen and the combination regimen may proceed independently. If patients achieve a CR during the first cycle of chemotherapy plus

5613, they will then receive 5613 as monotherapy to complete a total of 84 days of treatment; otherwise, they'll receive a second cycle of chemotherapy plus 5613, and then return to monotherapy to complete the treatment period.

Children may continue 5613 until progression of disease with unacceptable toxicity. The study design may allow us to identify different MTDs and RP2Ds for the monotherapy and combination regimens and provides children with the best opportunity for clinical benefit.

For 5613 monotherapy, DLTs will include events not clearly related to the underlying disease. Specifically, any such grade 3 or greater non-hematologic toxicity, or any non-hematologic toxicity that results either in discontinuation or interruption for more than 7 days, or in administration of less than 75 percent of the plan dose intensity during the first cycle, will be considered a DLT. Grade 4 neutropenia or thrombocytopenia that persists in the absence of residual leukemia will also be considered a DLT.

To identify a dose of 5613 that can be combined safely with toxic chemotherapy, we're proposing a definition of dose-limiting toxicity based on the concept of functional DLT criteria. This approach has been used in several COG studies in which targeted agents have been combined with backbone chemotherapy.

Specifically, the following events will be defined as DLT events, defined as DLTs that are attributed to 5613 alone: most grade 4 non-hematologic events, selected grade 4 or grade 3 non-hematologic toxicities, and grade 4 hematologic toxicities that are commonly observed with chemotherapy but if, and only if, they delay administration of the next cycle of therapy for at least 14 days.

In summary, given the poor prognosis and limited treatment options for children with MLL-r leukemias, development of new targeted agents should be rapid and efficient to serve the needs of these woefully underserved children. SNDX-5613 has robust therapeutic potential for children with

genetically-defined acute leukemias. As such, the potential benefits of immediately beginning a phase 1 trial that incorporates a combination with chemotherapy as a therapeutic option far outweighs the risks.

Thank you. We're happy to take your questions and value your feedback.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you very much for your presentation.

We will now take clarifying questions for Syntax Pharmaceuticals. Please use the raised-hand icon to indicate that you have a question. Please remember to put your hand down after you have asked your question. Please remember to state your name for the record before you speak.

It would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with "that is all of my questions" so we can move on to the next panel member. I will limit the number of questions to a 10-minute window since we are behind, so we will

start with questions.

I see Andy Kolb.

DR. KOLB: Thank you, Alberto, and thank you, Mike, and to Syndax. I think your urgency in testing in kids is to be applauded, as well as your compassionate-use program, so thank you for that and for the presentation.

I have several questions, but I think to start, in phase 1 design, I think your experience with the pediatric patients that were tested in compassionate use is consistent with what we would expect with a KMT2A mutated AML, and that is that the disease will be rapidly progressive; and single-agent, differentiation agent, it may be difficult to complete a 28-day course.

I'm wondering if in that monotherapy design, the requirement for a 28-day evaluation period I think is going to be difficult and how you plan to address that if you see a lot of kids going off onto the combination.

Then I'd also be curious to know -- I know you're pursuing NPM1c mutations in adults. That's

about 9 percent of pediatric AML, but they tend to do well, whereas we have NUP98 fusions, which are about 2 percent of pediatric AML, and they do poorly. So you may see as many relapsed NUP fusions as you see NPM1c in pediatrics, and if you have any interest in looking at other fusions like NUP98 that activate HOX proteins.

Thank you. That's the end of my question.

DR. MEYERS: Dr. Kolb, thank you for your comments and your questions. We recognize that it is distinctly possible that children will progress rapidly, and that is why we believe that the ability to transition them to chemotherapy is in fact the reasonable option.

However, we believe that, based on our preclinical data and are emerging clinical data, there is also a distinct possibility that children may in fact show single-agent activity early on; if not responses, at least control of disease that would allow them to stay on treatment for the 28-day period.

Obviously, if they don't, and they

transition to chemotherapy, we will be studying the safety of 5613 in chemotherapy, and we would propose to impute any child who gets through 28 days of combination chemotherapy without a DLT as being indicative of the fact that they would have gotten through the 28-day period of monotherapy without a DLT as well.

What I would add to the second question of NUP98 is we have heard of preclinical results indicating that there may well be activity in NUP98, which is a nuclear-pore protein, and we are in fact examining those further and would consider adding them into our phase 1 or phase 2 pediatric trial at a later time.

DR. KOLB: Thank you.

DR. PAPPO: Elizabeth, you're next.

DR. RAETZ: This is Elizabeth Raetz from NYU. Thank you, Dr. Meyers, for your excellent presentation, and I echo many of Andy's sentiments as well. I had some additional questions just in terms of your proposed pediatric trial as well.

I just was wondering, in terms of what you

proposed for the chemotherapy combinations, if there were preclinical data to specifically inform the recommendations for those specific agents. That was one question.

In your plan trial design, you mentioned that you may have to consider the infant population separately because of unique issues with dosing and toxicities, et cetera, so I didn't know if it was envisioned if infants would be a part of the trial.

A third question is, in terms of your plans for the DLT evaluation, I was wondering if the ALL patients and AML patients would be evaluated separately or the same for toxicities, as they may differ in their disease states coming in and may potentially receive different combinations.

Then finally a fourth question, and I apologize if I missed it, will PK data that you obtained over the course of the trial be used in a real-time way to optimize the dosing? Thank you.

DR. MEYERS: The chemotherapy regimens that we propose to use are typical salvage regimens for AML and ALL. There were two specified regimens.

One would be 2 cycles of FLA in patients with AML or selected patients with ALL -- or a typical 4-drug regimen such as I believe was used in block 1 of your trial published in 2008 in patients with ALL -- would also have an option to receive 2 cycles of FLAG, of FLA.

In terms of preclinical data, we are currently generating those data with typical chemo combinations, as well as with other agents such as venetoclax, CLT3 inhibitors, and hypomethylating agents. We don't have them yet, but we don't actually believe that they are gating to beginning our phase 1 trial because the positive predictive value of those preclinical studies is fundamentally compelling.

In terms of infants, we will be including infants in our phase 1 trial. As I said, we would be including children as young as 1 month of age up to 21 years of age. My comment about needing to treat the infant separately was based on basically the phase 2 trial.

The DLT criteria will not differ between

ALL and AML. What we are seeking to do is simply subtract out the specific toxicities that are common to whatever chemotherapy regimen the child may be receiving in determining what our DLTs are, but we would prefer to have a single maximum tolerated dose or RP2D for 5613 in combination with any number of chemotherapies.

We realize that we may actually underestimate the maximum tolerated dose, and we do certainly think that in the future we could actually use PK adjustments to better refine the dosing that patients would receive in phase 2 trials with the potential for intrapatient dose escalations in phase 2.

I think that answered all your questions I hope.

DR. RAETZ: Yes. Thank you so much.

DR. PAPPO: Julia?

DR. GLADE BENDER: Sorry. This is Julia Glade Bender from Memorial Sloan Kettering. I was going to ask a question along the lines of Elizabeth Raetz, and ask about intrapatient dose

escalation; because I think that the dose-response data that was presented is very compelling, and I wondered truly if during the single-agent phase, if a patient were not rapidly progressing, whether they would be able to intrapatient dose escalate and continue on the single drug therapy.

DR. MEYERS: Yes, we're definitely considering the possibility to interrupt patient dose escalation, but only after a patient satisfies the DLT window, since if we escalated within the first 28 days and the patient experienced a DLT, it would be difficult to determine which dose was responsible for that DLT. But this is certainly something that we are considering and proposing.

It's actually an element of our phase 1 adult trial, and we have also discussed the possibility of doing intrapatient escalations based upon PK, although that's not widely accepted by some of the institutions at which we will be conducting our phase 1 trial.

DR. PAPPO: Okay. Steve?

DR. DuBOIS: Steve Dubois, Dana-Farber,

Boston Children's; two questions. One, for adults with QT prolongation, were there confounding factors such as other agents that prolonged the QT interval in those patients?

The second question, it's fantastic that you've already developed a liquid formulation of the agent for a disease where your target of interest is enriched in infants, so that's fantastic. I'm wondering what type of data you have supporting the equivalence of that liquid formulation compared to the pill formulation.

DR. MEYERS: So let me take the second question first if I might, and that is that we've treated children thus far in our compassionate use with an extemporaneous formulation, which is an aqueous formulation of API dissolved in water and delivered through a syringe. We've shown compatibility in NG-tubes and G-tubes.

The API in 5613 in fact is rapidly soluble in a variety of aqueous solutions with a variety of pHs, especially in gastric pH, and therefore we do not perceive that there will be a problem with

equivalency between the capsules. The extemporaneous oral solution that we're currently using and the pediatric formulation, which is also an oral solution, that is well underway and will be available by the time we initiate our phase 1 trial in pediatrics.

The second question about QT prolongations, what we've observed thus far is that QT prolongations are related probably to Cmax. They appear very early in the treatment period, often within hours of the initial dose. We have looked at things such as concomitant medications, comorbid medical conditions, and electrolyte levels. Remember, this is a very small number of patients to date, and therefore those associations have not borne fruit, however, we will continue to look as we accumulate more data.

We are very aggressive in monitoring QT prolongations, and we also have a very aggressive and conservative dose interruption and reduction strategy for managing these both in adults and in children.

DR. DuBOIS: Thank you; no further questions. Thanks, Alberto.

Open Public Hearing

DR. PAPPO: Thank you.

I'm sorry, but we're going to have to stop the questions right now for the sponsor since we are a little bit behind schedule. We will now proceed to the OPH session.

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 open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

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

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

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for the open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect, therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

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

DR. GORE: Thank you, Dr. Pappo.

Good afternoon, committee members. My name is Lia Gore, and I am a pediatric oncologist at Children's Hospital Colorado. I also serve as the co-director of the Developmental Therapeutics Program at the University of Colorado's NCI-Designated Comprehensive Cancer Center; and earlier this year, I accepted the role as group-wide vice chair for the Children's Oncology Group.

The primary focus of my career has been in pediatric oncology drug development and phase 1 clinical trials, and I've been involved in the conception, design, and operations of phase 1 clinical trials in both pediatric and adult oncology for essentially my entire career.

I've served as an advisor to this committee, and I want to confirm that I have no financial relationships with Syndax Pharmaceuticals but did serve as the PI of a clinical trial of another one of their drugs in adult cancer patients more than 10 years ago. I'm here today of my own

accord as a pediatric oncologist with the resume as I've noted, and it's an honor to speak with you.

While the overwhelming success story in childhood cancer is really one of the outstanding cure rates seen in the large majority of children who have acute lymphoblastic leukemia or ALL, a subset of our patients still have a very poor prognosis, and many of the advances that we've observed in recent years have not translated to the clinical benefit for some of our most vulnerable patients.

In this group are our infants whose leukemias are often driven by the abnormal gene product involving the mixed-lineage leukemia gene, or MLL, which has now been renamed to KMT2A. The oncologists on this committee are well aware that KMT2A-driven leukemias, especially those in babies, are highly aggressive and highly therapy resistant. It's possible for patients with KMT2A rearrangements to go into remission, but they often relapse very quickly; and once that happens, their life expectancy is usually measured in days or

weeks.

KMT2A rearranged leukemias also have a unique plasticity that means they can morph between lymphoid and myeloid characteristics as the name MLL would suggest, but it means that the use of antigen-directed and other targeted therapies often do not provide the clinical benefit or lead to durable response that we see with other patients.

In brief, the therapeutic regimens we've used to date are essentially ineffective and have cumulative toxicities and are particularly devastating for very young babies who might survive. The combination of highly toxic and suboptimal effective therapies for infants with leukemia and for KMT2A rearranged leukemias overall is one of the most frustrating areas that pediatric oncologists deal with. Current chemotherapy strategies simply don't work for most of these patients, and even when they do, they impart significant life-threatening and even fatal side effects.

KMT2A rearranged leukemias are

exceptionally rare overall in incidence, which makes them very hard to study. Relevant to this discussion and patient population, I was the senior investigator on a phase 1 clinical trial with a single agent in KMT2A rearranged leukemias, which enrolled patients in select centers across the U.S. We learned a lot during that, and after the trial, about studying single agents in children with other highly refractory leukemias that we should consider as we think about the development of SNDX-5613, both what we should do and what we should not do in conducting these trials.

We need to be able to learn from studies conducted in adults to ensure that our clinical trials for children are safe and efficient. Given the rarity of this patient population, we must commit to constructing carefully designed clinical trials that maximize safety of patients while offering the best chance to be treated at a dose and schedule that could offer potential benefit and efficacy.

KMT2A rearranged leukemia, and in the past

40 years, we have made no significant progress. A menin inhibitor is what many pediatric oncologists have been waiting for based on the mechanism of action, and I feel it's critical to test this in children due to the unique biologic inhibition of KMT2A by this agent, as SNDX-5613 has the potential to fill a deep and significant void in our current treatment options for patients with KMT2A driven disease. Early adult data would suggest the potential for clinical activity, and every day we see children in our clinics who have no options for a realistic chance of survival.

We've learned over the last 15 years or so that many, if not most, biologically targeted agents that are used in adults with cancer have very similar dosing and toxicity profiles in children, and that often children can even have the same or fewer side effects compared to adults who are treated at the same doses and schedules.

I would very respectfully urge you to consider an efficient clinical development strategy of SNDX-5613 for children with KMT2A rearranged

leukemia in a way that allows the pediatric oncology community to explore this agent as quickly and is safe and reasonable on behalf of our most vulnerable patients, their families, and the oncology and scientific communities at large.

The patients we care for cannot wait for a conservative or a slow approach. Indeed, the past 40 years and more have proven this, and we need to do better. Thank you for listening to my comments.

DR. PAPPO: Thank you very much.

Speaker number 2, your audio is connected now. Will speaker number 2 begin on introduce yourself? Please state your name and any organization you are representing for the record.

DR. STEIN: Thank you very much. My name is Eytan Stein, and I am an attending physician on the adult leukemia service at Memorial Sloan Kettering Cancer Center. I also direct the program for Drug Development in Leukemia at Memorial Sloan Kettering, which is a dedicated phase 1 program for adult patients with leukemias and related diseases. I've previously participated in a paid advisory

board for Syndax, but I'm not being compensated for my appearance here today.

I've chosen to make comments to the committee because of my enthusiasm for menin as a therapeutic target in patients with acute leukemias with MLL rearrangements and because of my strong belief in the promise of differentiation therapy. I have a long-standing interest in MLL-rearranged leukemias, in part because of my work at Memorial Sloan Kettering where an unfortunate minority of our adult solid-tumor patients who received cytotoxic chemotherapy go on to develop therapy-related AML with MLL rearrangements.

In this regard, I led the phase 1 first-in-man study of the DOT1L inhibitor pinometostat in patients with AML or ALL, whose results were published in Blood in 2017. While we saw some interesting responses in patients using this agent, including clearance of extramedullary disease and one cytogenetic remission, too few patients responded to continue further development as a single agent in MLL-rearranged leukemias.

Newer therapies are crucial to eradicate this particular subset of acute leukemia.

My interest in menin as a therapeutic target began with interactions I had with Dr. Scott Armstrong when he worked as the director of the Center for Epigenetics at Memorial Sloan Kettering. The preclinical data his group generated in cell lines and patient-derived xenografts, and published in Cancer Cell in 2019, demonstrated the feasibility and efficacy of pharmacologic inhibition of menin.

Inasmuch as preclinical science anticipates true clinical benefit, the data generated in that paper is more impressive than most, and because of this and other data published in the literature, our group actively sought out clinical grade compounds and companies to work with on the clinical development of menin inhibitors.

My clinical experience with menin inhibitors comes from treating adult patients with SNDX-5613 on the phase 1 study of patients with relapsed and refractory acute leukemias. Data

presented at the AACR meeting in 2020 showed an impressive response to single-agent therapy in a patient with relapsed and refractory leukemia, and while anecdotes are not data, I do want to share a personal story about a patient I'm currently treating on study.

This is a 58-year-old woman with therapy-related AML with a 911 translocation. She received induction chemotherapy, achieved a complete remission, and went on to receive an allogeneic bone marrow transplant from a haploidentical donor. She unfortunately relapsed within 3 months of her allograft, failed further salvage chemotherapy, and was referred to Memorial Sloan Kettering for consideration of participating in the study with SNDX-5613.

When I examined her at the initial visit, she had the most severe leukemic infiltration into her gingiva, leading to gingival hyperplasia that I have ever seen. Her teeth were nearly completely covered by her gums, to the point that her diet was limited to liquids and pureed food. In addition,

she was being maintained on high doses of hydrea for control of leukocytosis driven by a pronounced increase in absolute peripheral blasts.

When I saw her for her cycle 1 day 22 visit last week, she expressed to me how her swollen gums had melted away. Her absolute neutrophil count, undetectable when I first met her, had risen 4.8, and her peripheral blasts, hovering around 75 percent of presentation, had cleared from her blood. She is able to eat, feels well, and cannot stop thanking the research staff at Sloan Kettering for giving her the opportunity to enroll in this study.

In my 10-year career of treating adult patients with acute leukemia, I've been fortunate to be involved and lead phase 1 clinical studies for patients with AML, where the compound under study has subsequently been FDA approved for a particular subset of AML. Most clinical trialists have a sense early on in the clinical trial when they are dealing with a winning drug and a winning strategy, one like Atra for APL or IDH and FLT3

inhibitors for non-APL/AML.

The preclinical data, early clinical data, and my personal experience as part of the SNDX-5613 study suggests to me that menin inhibition is likely to profoundly change the poor outcome for patients with MLL-rearranged leukemia. Although I'm not a pediatric oncologist, as an adult oncologist and a parent, I strongly advocate for pediatric patients with MLL-rearranged leukemias to have early access to menin inhibitors as part of a well-designed clinical trial. Thank you for taking the time to listen to my comments.

DR. PAPPO: Thank you very much.

Speaker number 3, your audio is connected now. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. BROWN: Sure. Hi. My name is Pat Brown. I'm a pediatric oncologist at Johns Hopkins in Baltimore. For the last 15 years or so, I've had led the clinical trial portfolio for infant ALL the Children's Oncology Group, and I'm also a

physician scientist with a research lab studying the biology of infant leukemia. So I've seen firsthand how the current treatment of babies with leukemia works or more commonly doesn't work.

Infant leukemia fortunately is rare with about 150 to 200 new cases per year in the U.S., and about two-thirds of these are BNH [ph] ALL and about a third are AML. As you've heard, most infant leukemias carry genomic rearrangements involving the MLL gene, the chromosome 11q23, and these cases have the worst prognosis of any childhood ALl subset, with a survival of 35 to 40 percent and a median survival of just over one year.

As survival for virtually every other subset of childhood, acute leukemia has steadily increased over the decades, including pH-positive ALL with the addition of TKIs, the dismal survival for infants has not budged. We've pushed chemotherapy intensity as far as it can go and stem cell transplant has not improved outcomes.

You heard that MLL leukemias are driven by

fusion of the normal MLL gene to one of many partner genes. MLL fusions are among the most potent oncogenes in cancer; hence, the extremely short latency between the acquisition of diffusion in blood precursors and the development of full-blown aggressive acute leukemia only weeks to months later.

One of the critical co-factors for MLL is menin. The physical interaction of menin and MLL is absolutely required for MLL fusions to drive leukemia in mouse models. Small molecules like SNDX-5613 that disrupt the MLL menin interaction have been discovered, and you've heard about the promising preclinical activity, adult phase 1 experience, and pediatric compassionate-use experience.

Infant ALL is a glaring unmet clinical need. Of the investigational approaches available, SNDX-5613 is the one about which we in the infant leukemia field are most excited. While immunotherapy that targets B-cell antigens like CAR-T cells, bites, and antibody drug conjugates

are great options for older children and young adults, unfortunately, infants are less likely to benefit.

Infant ALL cells express CD19 and CD22 antigens at lower levels; sometimes not at all, and with treatment, these leukemias often undergo lineage switching from lymphoid to myeloid and lose expression entirely. In addition, failure to manufacture a CAR-T cell product is common when it is attempted in infants. The trials that led to FDA approval for CAR-T cells only included patients 3 years of age and older.

Our two recent attempts to improve outcomes for infant ALL with targeted small-molecule approaches, mainly FLT3 inhibitors and DOT1L inhibitors, did not succeed, which was heartbreaking. We know now that this failure was primarily due to pharmacological mutations and inability for these drugs to potently inhibit the target in patients. We're very hopeful that's SNDX-5613 can overcome these limitations based on its superior pharmacologic properties both in

preclinical models and in the preliminary clinical experience in adults.

One final point, it will be exceedingly important to study SNDX-5613 in combination with chemotherapy in early-phase studies for two reasons. First, at the time of developing refractory disease or relapse, these leukemias are strikingly aggressive and proliferative. Second, since SNDX-5613 works to regulate gene transcription and will likely take time, perhaps 2 or 3 weeks, to demonstrate its maximal entire leukemic effect, I strongly urge regulators to set a low bar for allowing us to treat babies with combinations of chemotherapy and SNDX-5613 in infants.

Single-agent safety and biologic/clinical activity in adults should be sufficient. The CAG ALL committee is developing a trial concept of this strategy currently. There is precedent for this. The very first clinical experience with FLT3 inhibitors and infants was in combination with chemotherapy for newly diagnosed disease in the CAG

ALL EURO-631 study.

In summary, I enthusiastically support aggressive pediatric clinical development of SNDX-5613, and in particular for infant ALL, which is uniquely dependent on the MLL menin interaction and continues to have a dismal prognosis with no advances in decades. Thank you.

Questions to Subcommittee and Discussion

DR. PAPPO: Thank you very much.

We will now proceed with a charge and questions to the subcommittee and panel discussions. After each question is read, we will pause for any questions or comments concerning its wording, then we will open the question to discussion. We will start with the first question from the FDA.

(Pause.)

DR. PAPPO: Would you like to read the question?

DR. REAMAN: This is Greg Reaman. I'll read these questions. The first discussion item for the committee is to consider the adequacy of

evidence of activity and lack of serious acute toxicity given the timeline of development of SNDX-5613 in adults to date to support the development of this product 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.

I don't see a lot of hands. Andy?

DR. KOLB: Thank you, Alberto.

This is Andy Kolb from Nemours A.I. duPont Hospital for Children. It took me a while to respond because I wasn't sure if this was pro or con for rapid development. It appears to me in the adult literature and the compassionate-use data that's available from pediatric patients, or the adult trial and the compassionate-use data, that the safety profile is favorable for this drug, either monotherapy or in combination.

As Dr. Gore and Dr. Brown so eloquently put it, I think that this is a population of patients that, for whom were quite risk tolerant, survival is poor in infants with KMT2A mutated ALL and AML,

and survival is poor in any KMT2A mutated relapsed patient. We tend to be quite risk tolerant in these patients who need aggressive therapy to get back into remission and in aggressive therapy consolidation with bone marrow transplant to ensure survival, and both are absolutely necessary for survival.

I think the cooperative groups and most sites that participate are very experienced in giving novel agents in combination with intensive therapy for patients with these disease types. Thank you.

DR. PAPPO: Malcolm?

DR. SMITH: Thank you, Alberto.

Malcolm Smith, NCI. I would agree with all the speakers that this is an agent that warrants fast-tracking for evaluation in children. It really checks all the boxes. Adults appear to tolerate the agent at doses associated with activity. It targets a genomic alteration that's a clear driver for a high-risk subset of pediatric leukemias, the functional genomics for all the

targeted agents. And the preclinical data to support it really shows profound activity. That a treatment course with a single agent in these very aggressive PDX-MLL rearranged models can induce complete remissions that last for hundreds of days is really a remarkable level of preclinical activity.

I think the thing that I would say that builds on that would be in thinking about how to use this in combination, this is an agent where SNDX-5613 will probably be the most active agent of any of the agents in the combination. So often we think of adding an agent to a combination, and we have to use the most aggressive toxic therapies because these are high-risk patients.

I think the possibility that -- this is a very active agent for MLL-rearranged leukemias, and the idea that the best way to use it in combination is to use it at a full dose and then add in the chemotherapy that we can, and really achieve the full benefit of using this agent. I think Dr. Stein's remarkable example in the patient that he

treated shows that this agent really could be transformative. Thank you.

DR. PAPPO: Thank you very much, Malcolm.

Elizabeth?

DR. RAETZ: Sorry. I was just going to echo those same sentiments and just add to that, that there has been great precedent for adding these novel agents in infant leukemia, as Dr. Gore and Dr. Brown so eloquently pointed out. My other points were covered by Dr. Smith and Dr. Kolb. Thank you.

DR. PAPPO: Thank you.

Let me see if anybody else has raised their hand.

Malcolm, do you have a follow-up question or comment?

DR. SMITH: I'm sorry. I don't. I'll lower my hand.

DR. PAPPO: Well, what I've heard so far is there is overwhelming enthusiasm about this very active and promising agent, and it meets the criteria for fast-track evaluation in children with

MLL-rearranged leukemias. It meets all of the criteria of almost an ideal agent. It has a very favorable safety profile. It targets a specific driver in MLL-rearranged leukemias.

There's strong preclinical and functional genomics to further validate its activity, and I think one of the issues is how do we incorporate this agent into combination therapy. Whether we start with the agent alone or we combine it with chemotherapy is something that needs to be determined.

But some of the panel members believe that perhaps the most active component of the therapy will be actually this agent, this Syndax agent.

Did I miss anything or did I condense all of your thoughts correctly?

(No response.)

DR. PAPPO: It sounds like I did good.

Let's go to question number 2.

DR. REAMAN: The second discussion topic, please consider the adequacy of the currently available PK data in children from the

compassionate-use experience in an attempt to model exposure/response after the adult recommended phase 2 doses been defined and demonstrated to be active.

Consider some alternative strategies for efficient recommended phase 2 dose definition in children and also consider the effect of strong CYP3A4 inhibition on possible activity and the high likelihood that many infants will be on such endeavors.

DR. PAPPO: Andy?

DR. KOLB: Thank you, Alberto.

This is Andy Kolb from Nemours Alfred I. duPont Hospital for Children. The two different cohorts in the phase 1 trial in adults is interesting. Having the CYP3A4 cohort and the non-CYP3A4 cohort I think is interesting. I do think that the fastest way to a phase 1 or recommended phase 2 dose in an efficacy signal in pediatrics could be to use alternatives to the azoles in this population wherever possible, and that may simplify the trial.

I still think we need PK data because azole use is so common, but with active alternatives out there or even moderates CYP3A4 inhibitors, it would be nice to see a slightly more simplified design in pediatrics to get to a recommended phase 2 dose in an efficacy signal as quickly as we can. I'd be curious to hear other's thoughts on given the common use of these inducers. Thank you.

DR. PAPPO: Leo?

DR. MASCARENHAS: Hi. This is Leo Mascarenhas from Children's Hospital Los Angeles, and I didn't get to ask this question earlier, but I think it's relevant to this discussion.

Given the prominent role of CYP3A4 and the metabolism of this drug, and the fact that newborn infants have really low levels of CYP3A4, and they reach about 50 percent of adult levels between the ages of 6 to 12 months, I wonder about automatically assuming whether the adult recommended phase 2 dose would be acceptable in those less than one year of age.

I don't think I have concerns above one

year of age, but I wonder whether a rapid intrapatient escalation should be considered to make it the safest possible way, as well as the most efficacious.

My second comment -- and I apologize if I missed this -- is infants with ALL do have a high incidence of central nervous system disease, and I wonder about the penetration of this drug or the biodistribution. I don't know if anybody has any information about that, and that may be a consideration. Thank you.

DR. PAPPO: Thank you.

Does anybody know the answer to Leo's question about the CNS penetration of the same SNDX compound? Something that we will put on the -- I'm sorry. Go ahead, please.

(No response.)

DR. PAPPO: We'll just put this on the minutes, then.

The next panelist is Julia.

DR. GLADE BENDER: Good afternoon. Julia Glade Bender. Again, I'm going to focus on getting

rapidly to the dose for children because I think there's a very high likelihood that this targeted agent may very well be the most active agent in these children, and more often than not when we do a stripped dose-finding phase 1 experiment and get our PK after the fact, we find that our toxicities were actually not related to the pharmacokinetics of the agent and were probably idiopathic.

So I would ask the company if they can think about a strategy of real-time PK to get individual children who enroll on the study to an exposure that they believe will be associated with response, and perhaps the dose finding could be the target exposure level and not so much the amount of drug that was given to the patient. Thank you.

DR. MEYERS: Dr. Pappo, may I address the questions Dr. Mascarenhas asked because I do have the answers to them?

DR. PAPPO: It is my understanding that at this stage you are not allowed to address the panel. That's what I know.

Greg, do you agree?

DR. REAMAN: I think it would be important for the discussion to know about the CNS penetration. I think it's extraordinarily pertinent to our discussion here with --

DR. PAPPO: Okay. Please go ahead. Then please go ahead.

DR. MEYERS: Thank you for that opportunity. So we don't know the extent of 5613 brain penetration in animals or humans. Those studies are planned in animals. However, based on the size and physicochemical characteristics of 5613, we predict that there's probably a low probability of brain penetration.

There's a so-called multiparameter optimization score, quote, "an MPO score" that predicts brain penetration, and ours is lower than would predict a high probability of brain penetration. That being said, prophylaxis and treatment of CNS disease is allowed in our pediatric phase 1 trial.

The second question that was raised was about CYP3A4 inhibition, and we would just cite a

paper by Eupretti [ph] et al. in 2016, suggesting that CYP3A4 reaches adult levels or higher in infants 1 month of age, by 1 month of age. We realize that is in contrast to the conventional wisdom, however, we do think that it may represent important data to consider in terms of deciding the lower limit of children included on the phase 1 trial.

DR. PAPPO: Thank you for those clarifications.

Anybody else have any additional comments or wants to raise their hand? I still see Julia and Leo. I don't know if you had additional comments or you just forgot to lower your hand.

I have Greg.

DR. REAMAN: I would just thank Dr. Meyers for that information about the CNS penetration, which I think is an important consideration here. I think there's also some considerable variability with respect to CYP3A4 maturation. It may be that would be a requirement for a pharmacogenetic evaluation for the youngest patients being

considered for enrollment on the study as well.

I just want to comment also on Dr. Glade Bender's comment about real-time PK. It sort of dovetails with the sponsor's comment about evaluating QTc prolongation and a strategy of dose reduction or dose interruption and whether or not evaluating PK in that setting in the real-time fashion would actually be something that would prevent automatic reductions and interruption given the fact that it looks like continuous exposure to this agent is required for either in nonclinical or clinical efficacy.

DR. PAPPO: Thank you.

Any other clarifying comments or questions? Julia?

(No response.)

DR. PAPPO: I don't know if you had a follow-up comment, Julia, or no.

DR. GLADE BENDER: Yes, just in response to Dr. Reaman and for purposes of discussion, I think what is compelling me to really consider intrapatient dose escalation is the clear evidence

that in 6 out of 6 children in the SPU situation, the compassionate-use situation, not one of them achieved a drug exposure that was anticipated to be associated with response.

So my point is just to make sure that patients are in the exposure level we anticipate to be response, worthy of response, or able to achieve response, because the idea of treating children long-term and in combination with chemotherapy when they're taking this drug, and it's not even achieving exposure levels that we anticipate will be associated with response, doesn't seem the right thing to do to me, to continue a drug that is not being given in an adequate dose to obtain exposures that would be associated with response.

DR. PAPPO: Greg?

DR. REAMAN: Just to clarify that, there's no argument, I don't think on our part, about your comment. That was part of the reason for the first question with respect to the extent of the pharmacology data from the expanded access program in children

and how sufficient that may be in actually developing a dosing strategy for a pediatric study.

DR. PAPPO: Thank you very much.

Tobey?

DR. MacDONALD: Tobey MacDonald, Emory University. I wanted to ask this question, and then here I'll comment, which I think might be relevant to question 2 and 3, and apologize if I missed it. But I was curious whether there was any ability to measure, in the clinical studies, biomarkers predictive of response that could complement the PK hand-in-hand in real time, such as HOXA transcriptional changes or other biomarkers of response to confirm on-target effects are being observed and mediated by the drug.

I think that goes to question 3 later, where obviously cell kill in remission, but if we have other therapeutic agents to ensure that the drug is working as anticipated. So I didn't know if there were any correlative biology studies planned for this trial. I didn't see it but, again, maybe I missed it and defer to my leukemia

colleagues, who are experts.

DR. PAPPO: I'm okay.

DR. MEYERS: Dr. Pappo?

DR. PAPPO: Yes? Go ahead, please. Go ahead.

DR. MEYERS: Actually, there is a slide AA-52 that addresses that question. We absolutely agree with Dr. MacDonald's point. In both the adult trial and the pediatric trial, we have aggressive pharmacogenomic marker assessments that are actually paired with our PK assessments.

For example, we will be obtaining, on day 1 and 8 from peripheral blood ChIP-seq to establish menin chromatin interactions. As I noted menin dissociates from chromatin when it is bound to 5613. We will also be doing RNA-Seq in bone marrow to determine the HOXA and NIS1 gene expression profiles, as well as any others that may evolve as we look at the activity of the drug in humans.

So we are very mindful of the fact that we do need to develop pharmacodynamic markers that can at least allow us to make judgments as to the

adequacy of RPK coverage. Thank you for that question and the opportunity to answer.

DR. PAPPO: Thank you.

I think that, Greg, you raised your hand again.

(No response.)

DR. PAPPO: Greg, do we have any additional comments or questions?

(No response.)

DR. PAPPO: The hand has been lowered, so the answer is no.

So if there are not any additional questions, I think a lot of the questions that were raised by the panelists were adequately addressed by Syndax. The only thing I wanted to add were a couple of comments, one from Andy in which perhaps limiting the use of azoles could address the issue of CYP3A4 interactions.

Also, given the variation and the maturation of the CYP3A4 pathway, it is still debatable, at least in my opinion, which is the optimal cutoff of age for enrollment, whether it's

one month of age or older or older than 1 year of age. The issue of real-time PK has been raised a couple of times, and perhaps considering intrapatient dose escalation to optimize dosing and achieve the levels that are necessary for inhibition of MLL and menin.

I don't know if I've left anything our or if anybody else wants to add anything to what I've said.

(No response.)

DR. PAPPO: Okay. We will then proceed to question number 3.

DR. REAMAN: Question number 3 for the discussion, given the adult experience to date and the requirement for extended continuous dosing to achieve a response, consider how the activity of SNDX-5613 might be assessed in a single-agent setting in a disease characterized by very aggressive clinical course relapse.

Given the adult experience with added cytoreductive therapy, consider the potential development strategy using relapsed therapy

backbones that may have previously been used even prior to enrollment on a study with SNDX-5613 in both KMT2A rearranged ALL and AML, as well as mixed phenotype leukemia.

DR. PAPPO: This question is now opened for comments. Some of these issues have been discussed a little bit in question number 2, but I think there are other things to address.

Andy?

DR. KOLB: Hi. This is Andy Kolb from Nemours Alfred I. duPont Hospital for Children. I do think that this is a key question and one that all of us are struggling with as we think about the development of this compound. In first relapsed AML with a KMT2A mutation with conventional therapy, the CRA is probably close to 70-75 percent, so demonstrating a benefit above that is a challenge. Overall survival is around 40 percent in KMT2A rearranged leukemias that experience a relapse, but time-to-event analysis with a historical comparator is not usually reviewed favorably.

I know in the Syndax presentation, there was a mention of a randomized trial, which I think we don't have -- forgive the pun, but we don't have the patience or the patients for, both spellings of the word. This is a rare subset of a rare disease, and I think given the enthusiasm around this trial, it would be difficult for investigators to consent to a randomized trial.

We need to think about this as a single-arm study with effective backbone therapy to control very aggressive disease, and we need to consider meaningful assessments of efficacy, and I think the most meaningful is survival. We have many kids who go into remission who don't survive. Ultimately, we need to improve survival in these kids.

Given the time constraints, I didn't have an opportunity to ask this previously, but as a comment for Syndax, regardless of the induction of remission and the rapidity of that, the next step for these patients is transplant. So in assessing the safety of this drug, I think we have to consider post-transplant administration as well.

You may only have time for 1 to 2 cycles pre-transplant, especially while we have limited experience with this compound.

Meaningful exposure to the drug will require post-transplant administration, and with that we may be able to see dramatic improvements in survival given the activity we expect with this drug. We just need to make sure that survival is an acceptable endpoint when compared to a historical control. Thank you.

DR. PAPPO: Elizabeth?

DR. RAETZ: Elizabeth Raetz. I think in terms of the infant ALL population, as pointed out by Dr. Gore and Dr. Brown, their ability to be salvaged is so poor, and responses in the relapsed/refractory setting have been so poor that I think even an opportunity to look early on as to whether you can achieve a remission might be [indiscernible] information.

Designs that have been utilized previously with a monotherapy window and to have some sense of the pharmacodynamic and pharmacokinetic, and

responses to early activity to the single agent followed by the combination, and then looking at the ability comparatively to achieve a remission to a comparable historical control might be something that would provide some useful information. Thank you.

DR. PAPPO: Thank you.

Malcolm?

DR. SMITH: Thank you, Alberto.

Malcolm Smith, NCI. I wanted to make a general comment about the potential for randomization. Andy makes a good point that there may be populations for which randomization wouldn't be possible, but I think as a general principle, randomization will be preferred in evaluating a new treatment to understand efficacy and toxicity.

But for these small populations, the ability to conduct a randomized study can be jeopardized by requiring very stringent type 1 error rates. There are unintended consequences to applying stringent type 1 error rates that would apply, and the adult much larger cancer populations

to these small pediatric populations, I think they can make the trials infeasible. They can delay answers to questions and they block alternative options because these are small populations, which in North America, only one new treatment option can be studied.

So to the extent that there will be randomized studies of this agent in one or more populations, I think relaxing the type 1 error rates, and instead of the conventional .025 one-side type 1 error rates, accept the 0.05 or 0.2 as a way to get a randomized study accomplished and get an answer for this very small pediatric population.

I would encourage -- we want to have more effective treatments in the relapsed setting, and that's where we test new strategies first. But our ultimate goal is to cure children the first time around, so to do what we need to do in the relapsed setting, but then as quickly as possible move it up front. Move the treatment strategies up front for the infant ALL population as well as for the AML

populations with the MLL-rearranged. So those are the two points I would make.

DR. PAPPO: Thank you very much. I had a question and comment also. I don't know what the median time to response was because I think that would be very important to determine how long you would give this as a monotherapy.

I was going to follow up on Elizabeth's observation. I think that doing a small quick window, maybe a week or two -- I don't know exactly how quickly you see responses to assess PK. If you wanted to do a specific PK and intrapatient dose escalation to achieve the levels that you want to achieve, it would be ideal, followed quickly by combination therapy. But again, I think that would be highly dependent on how quickly the leukemia is progressing and when do you expect to see a response with this drug. So that was the only other observation I had.

Malcolm?

DR. SMITH: I did want to respond to that, Alberto. I think in terms of the rapidity of

response, I think you heard from Syndax a response that occurred in the first course. You heard from Dr. Stein a response that occurred quickly. In the PDX models, while there could be increasing blast in the first week of treatment, by day 1, in almost all the models tested, the blast levels had markedly decreased.

So I think this is an agent that is capable of marked early responses, and I think we just have to see when we treat children at doses that achieve the levels that we want.

The additional one point I want to make is this. We have two recent models from ALL phase 3 trials for improving outcomes for children with ALL. One is for imatinib, where imatinib was given throughout therapy and improved outcome for the pH-positive ALL. The other is from nelarabine for T-ALL, where it was given interspersed with conventional therapy, and it as well improved outcome.

So I think there will be things to think about as we understand the agent more and we

understand how well it's tolerated in combination and how active it is as a single agent. I think the people designing the studies will need to think about the best approach in bringing this into our upfront treatment for pediatric ALL and pediatric AML.

DR. PAPPO: Thank you, Malcolm.

I don't see any other hands. Does anybody have any additional comments or questions? Greg?

DR. REAMAN: I just want to respond or follow up on Dr. Smith's point about nelarabine and the strategy that was used as a single agent and then in combination. Before that combination strategy was employed, there was pretty robust evidence of activity clinically, but single agents.

So the situation is not quite the same here, although the situation with respect to the prognosis of relapsed patients is probably very similar. But I think before moving to combination, there was really very strong evidence of single-agent activity in nelarabine and T-cell acute leukemia.

DR. PAPPO: Thank you, Greg.

I think some of the questions were answered either by the sponsor or by Malcolm regarding when do you achieve a response, and also the correlative studies and biomarker studies to try to address the efficacy of this treatment. The optimal combination is still to be determined. One of the considerations will be also to assess the efficacy of this agent to establish overall survival as an endpoint.

There was some concern about randomized studies given the small population, however, perhaps looking at the statistical design and relaxing some of the statistical endpoints would allow for this to be done. Also, if this proves to be efficacious and the relapse happening, to think about moving this relatively quickly to upfront therapies.

I think that's all I have unless I'm missing something.

Greg, you have your hand raised. Is there anything I missed, or anybody, or anybody else

wants to add anything?

DR. REAMAN: No. I'm sorry. I forgot to lower it again. I apologize. I think that was all.

DR. PAPPO: Are there any additional comments? If not, we'll move onto Greg Reaman for closing remarks.

Closing Remarks - Gregory Reaman

DR. REAMAN: Well, my only closing remark is, again, to thank you the panel for the excellent discussion, and Syndax for their presentation of a uniquely interesting novel agent that I think we all unequivocally agree addresses one of the biggest unmet clinical needs in pediatric oncology.

So thank you all for the discussion and also for your flexibility and patience again with doing this pediatric subcommittee meeting in a virtual setting. Hopefully this won't be the everlasting normal, but then again, maybe it will. I think despite all the difficulties that we envisioned, I think things actually went pretty smoothly from a technological perspective. So

again, I want to just thank you all very much; very helpful.

Adjournment

DR. PAPPO: Thank you very much, Greg. I would like to also, once again, thank Dr. Bonner and also the staff at the FDA for making this happen. It went very, very smoothly, so once again, thank you very much. And thank you to the panel for joining us and to all the presenters, and we will now adjourn the meeting. Thank you very much.

(Whereupon, at 3:05 p.m., the afternoon session was adjourned.)