FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

Topic 2

Thursday, June 22, 2017

10:26 a.m. to 11:45 a.m.

FDA White Oak Campus

The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

P R O C E E D I N G S

(10:26 a.m.)

DR. PAPPO: Good morning. We will now proceed with topic number 2, prexasertib from Eli Lilly and Company. Dr. Lauren Tesh will read the conflict of interest statement for this session.

Conflict of Interest Statement

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

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

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

being provided to participants in today's meeting and to the public.

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

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes

of 18 U.S.C. Section 208, their employers.

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

This session's agenda involves information to gauge investigator interest in exploring potential pediatric development plans for two products in various stages of development for adult cancer indications. The subcommittee will consider and discuss issues concerning diseases to be studied, patient populations to be included, and possible study designs 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 prexasertib, presentation by Eli Lilly and Company. This is a particular matters meeting, during which specific matters related to Eli Lilly

and Company's product will be discussed. Based on the agenda for today's meeting and all financial conflicts of interest 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. Leo Mascarenhas and Brenda Weigel.

Dr. Mascarenhas's waiver involves his employer's current study of prexasertib, funded by Eli Lilly, which is anticipated to be between $0 and $50,000 in total funding. Dr. Weigel's waiver involves her employer's two studies of prexasertib, funded by Eli Lilly, which are anticipated to be between $0 and $50,000 in total funding per study.

These waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing these waivers are described in the waiver documents, which are posted on the FDA's website. Copies of the waivers may also be obtained by submitting written requests to the agency's Freedom of Information Division 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 have made concerning the product at issue.

With respect to FDA's 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 may 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, the FDA believes it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages all individuals and participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based upon the outcome of the meeting. Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not

have any such financial relationships.

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

Industry Presentation - Allen Melemed

DR. MELEMED: I would first like to thank FDA again for the opportunity to present our molecule to the pediatric advisory committee. Hello again. My name is Allen Melemed. I'm a pediatric oncologist, and I currently am responsible for the U.S. regulatory group for Eli Lilly and Company.

It is a pleasure to be here today to discuss prexasertib and get feedback from the committee on our development plan. Following me will be Dr. Lin, and she'll present the development of prexasertib for both adults and pediatric cancers.

I'm going to use this slide that you've seen before a slightly different way for prexasertib. With prexasertib, we are able to look at this drug

sooner because we already had started this collaboration internally to have these non-clinical models to study.

We studied prexasertib early when it was in its initial phase 1 and 2 trials. I still remember the hope and excitement when Lou Stancato shared with me the data from LY2880070, which is the data that Dr. Lin will share later today.

All of this is with the hope here that we can find new drugs that can help children with cancer, and we're now going to go on to the presentation for Dr. Lin to present prexasertib.

Industry Presentation - Aimee Lin

DR. LIN: Thank you, Dr. Melemed.

My name is Amy Lin, and I'm a research advisor at Eli Lilly and Company. And it is my privilege to be here today on behalf of the prexasertib team to present and want to thank you on behalf of the team, the committee, and the FDA for the opportunity to gain feedback on our pediatric development plan.

So prexasertib is a small molecule inhibitor

of checkpoint kinase 1. In 2010, its IND was opened, and in 2015, it was granted orphan drug designation for the treatment of anal cancer.

Currently, there are 12 ongoing or completed phase 1 or 2 trials, and since we're still relatively early in development, a PIP or PSP have not yet been submitted. Additionally, there are currently no CHK1-targeted agents that are approved, so the team is optimistic and excited about the opportunity for this molecule to have a novel way to potentially improve clinical outcomes for both adults as well as pediatric patients.

As Dr. Melemed alluded to, our interest in prexasertib is a therapy for pediatrics. It was sparked several years ago when across a panel of in vitro cell lines, shown here, the EC50 value, plotted here on a log scale, was markedly better than what was observed for standard of care agents.

We know that it's a long ways to go from a simple in vitro screen to an effective therapy for pediatric patients. But nevertheless, very early in development, this was the point that we started

to think about how should we approach pediatric development for this agent.

That plan then really forms the outline and the framework for my comments today. First, I'll review briefly the target and the molecule; then go through our adult clinical data, both monotherapy and what's ongoing in combination; talk about how we further extended our non-clinical data into more sophisticated models; review the study design of the phase 1 that's ongoing sponsored by the Children's Oncology Group, and how those data will then lead into our proposed study in relapse/refractory rhabdomyosarcoma or neuroblastoma.

We then look forward to getting your input, both on that proposed design as well as future places that we should start to think about either in monotherapy or in combination therapies.

So briefly, a word about the target. Checkpoint kinase 1 is a multifunctional cell cycle target. It plays a critical role in response to DNA damage at the intra-S or G2/M checkpoint. It's

integrally involved in homologous re-combination repair and is a negative regulator of DNA replication origin firing, and as such plays an important role in resolving replication stress.

As a result, it's been hypothesized by ourselves and by others that tumors that either have increased levels of replication stress or defects in DNA damage repair may be more sensitive to the effects of a CHK inhibitor such as prexasertib.

Prexasertib itself is a an ATP competitive inhibitor. In biochemical assays, it's very potent with a sub-nanomolar IC50 value. It's relatively selective, and when we look in non-clinical models, the phenotype that we observe phenocopies what is observed with siRNA knockdown of CHK1 and includes the disruption of the repair of DNA damage and replication and mitotic and replication catastrophe.

Data is currently available from two of our ongoing or completed studies. The first was the phase 1, the initial phase 1, where we treated

146 patients across dose-escalation and dose-expansion cohorts.

Although the primary objective of this study was to identify the recommended phase 2 dose, one of the striking findings was that durable objective responses were observed as a monotherapy in patients with either head and neck or anal cancer.

The reason that this was striking was, prexasertib was the first CHK inhibitor to demonstrate monotherapy activity. A paradigm in the field up until this point was that CHK inhibitors would have their greatest utility in combination with DNA damaging agents, and therefore would be predominantly chemopotentiators.

But we were able to demonstrate that sustained and potent inhibition of CHK can result in monotherapy results, and this has led now to a new generation of CHK inhibitors that are being evaluated both in monotherapy as well as combination.

In this trial, we also characterized PK, and perhaps looking ahead to some of the non-clinical

data we'll share, I want to emphasize that the clinical exposures that were achieved in this study are consistent with those that we observe in non-clinical models where efficacy is observed.

Finally, the recommended phase 2 dose was identified as 105 milligrams per meter squared when prexasertib is administered as a 1-hour IV infusion once every 14 days. The primary dose-limiting toxicities were all hematologic in nature, and indeed hematologic toxicity is the hallmark toxicity of this molecule.

Over 70 percent of patients will experience grade 4 neutropenia and to a lesser extent thrombocytopenia or anemia. But perhaps just as interestingly, the non-hematologic toxicities occurred in much lower incidence, with only fatigue, nausea, and headache occurring in an incidence of greater than 10 percent. And regardless of instance, the majority of non-hematologic toxicity is grade 1 or 2 in severity.

The data you're seeing here are from patients treated at 105 milligrams per meters

squared, the recommended phase 2 dose. Approximately 100 patients are shown, and these represent toxicities that were observed at any point during their therapy.

Perhaps the neutropenia bears just a bit of an additional word in that this is transient neutropenia. So the grade 4 neutropenia typically resolves within 5 days, and even though we have a relatively short duration cycle of 14 days, the vast majority of patients do not require dose reductions or dose delays.

In addition, G-CSF use may reduce both the extent and the duration of the neutropenia, at least in a subset of patients. And perhaps the combination of the combined use of G-CSF and the transient late nature of the neutropenia has led to acceptable febrile neutropenia rates of approximately 10 percent.

Data is also available from an ongoing phase 2 study that's sponsored by the NCI, looking at multiple cohorts of patients. Data from two of the cohorts, which enrolled high-grade serious

ovarian cancer patients, either BRCA mutant or BRCA wild type, were presented by the lead investigator, Dr. Jung-min Lee at ESMO last year.

In this study, when the aggregates of those two cohorts were combined from a safety perspective, you can see the safety toxicity profile mirrors that what we've observed in the phase 1 with hematologic toxicity predominating. It may be notable in this more homogeneous population that the febrile neutropenia rate was just 6 percent.

But what also caught our interest was the efficacy data. At the current time, data is limited from the BRCA mutant patient population, so it's difficult to draw conclusions about that cohort. But from patients enrolled in the BRCA wild-type cohorts, there were objective responses observed in 35 percent of the patients across both platinum-sensitive and platinum-resistant disease.

When we compare this to historical controls, this is more than twofold higher than what we would expect for this population and has generated some

interest and enthusiasm about how we may pursue this agent in patients with ovarian cancer.

Here then is a summary of the ongoing or completed clinical trials with prexasertib, all of which are phase 1 or phase 2. And while the focus of today's talk focuses on solid tumors and the majority of our program does, I'd be remiss if I didn't highlight that there is an ongoing study in patients with relapse refractory AML. And I think we're keenly interested in hematologic malignancies, both given the safety profile as well as some of the mechanistic underpinnings of prexasertib.

You'll also notice that a large portion of our clinical efforts right now are focused on combination therapy. And I think this represents one of the challenges for prexasertib development and that the agents, that from a mechanistic perspective are most attractive to combine with prexasertib, may also have overlapping hematologic toxicity.

So we're exploring cytotoxic chemotherapies

in our adult phase 1 program, but also looking at targeted therapies and radiations, as those may also be attractive combination partners that will have less overlapping toxicity.

But I think a particular challenge perhaps for pediatric development is that many of the agents that we're looking at in our phase 1 program in adults are not commonly used in the pediatric setting, so we recognize that we need to generate additional data there to understand both the optimal combination partners from a safety as well as efficacy perspective and are using non-clinical models to look at agents such as cyclophosphamide, doxorubicin, and irinotecan to try to inform what would be optimal combinations potentially in a pediatric setting.

But overall, with our data in the clinic right now, there's nothing that precludes us from moving forward with development in either a monotherapy or combination setting.

So I want to turn our attention now to some of the additional data that we've generated in non-

clinical pediatric models. In addition to the initial in vitro screening program, we've worked hard to expand our in vivo models that we have access to within Lilly.

Here's a subset of what we've looked at, and these demonstrate that prexasertib has the ability to induce regressions, either complete responses, denoted by CR, partial responses, denoted by PR, or stable disease, denoted by SD across a variety of neuroblastoma or pediatric sarcoma models.

We've also been working with external collaborators in both the academic setting as with the NCI to expand our experience. And in particular, our collaboration with the PPTC has been very productive, and we're grateful to them today for allowing us to share some of their unpublished data, looking at prexasertib as a monotherapy again in models of neuroblastoma or sarcoma.

When we combine these data, we observe that 9 out of 9 of the neuroblastoma models and 7 out of 10 of the rhabdomyosarcoma models have activity

following treatment with prexasertib. These data all represent monotherapy data, and we're continuing to extend and augment this with combinations with both cytotoxic as well as targeted agents.

Now, the tabular summary is nice because it shows an overview of what we've generated. But I think part of what's generated the excitement for us both internally as well as externally as we've talked to thought leaders in the field is the extent and duration of the responses that we see. So we wanted to show you a few representative examples of these xenografts.

Here, we plot days versus tumor volume, and they're plotted versus a vehicle control as well as a standard of care control. Treatment is initiated with the green arrows and stopped with the red arrows. And you can see that following the initiation of prexasertib treatment, there is significant regression in these models. These models, perhaps noteworthily, are both MYC and amplified models, which are obviously an important

prognostic factor within neuroblastoma.

MYCN has long been linked in the literature to a potential increased sensitivity to CHK inhibition. MYCN amplified models will have an inappropriate licensing of the replication forks. This leads to a depletion of nucleotide pools needed for DNA synthesis.

The ATR CHK pathway is one of the pathways used to compensate for that replication stress. So then when we add prexasertib, we inhibit CHK1, its response to replication stress, and potentially push the cells toward replication catastrophe.

But I also think these data may highlight another challenge for prexasertib as we are developing the molecule in that while each of these models are MYCN amplified, some of the other models where we did see pronounced responses were not MYCN amplified. Indeed, when we look in other settings and other histologies, MYCN amplifications do not necessarily correlate with this level of response.

So I think that this suggests that the tailoring and biomarkers used to predict

sensitivity to prexasertib are complex, and likely not a single marker will predict either resistance or sensitivity.

An ongoing area of focus for us is to try to identify what are those cadre of markers that will have that predictive power, but at the current time, we do not yet have the ability to prospectively predict which patients in the clinic will respond or be resistant to prexasertib.

In addition, we wanted to show you also representative models of both aRMS and eRMS where, again, the data is plotted in this same fashion. And you can see that following the initiation of treatments, these models also show regressions to prexasertib.

So these data, both the clinical data as well as the non-clinical data, then helped inform the Children's Oncology Group, which is sponsoring a phase 1 study. This again has been a very productive and fruitful collaboration, as they have recently initiated the trial just in March of this year.

Their study enrolls patients with either current or refractory solid tumors, including CNS tumors, and hopes to establish the maximum tolerated dose or recommended phase 2 dose of prexasertib as a monotherapy. In addition, they will characterize the toxicities, pharmacokinetics, anti-tumor activities, and biomarkers.

The starting dose for this study is 80 milligrams per meter squared, but data is not yet available from this study. However, as we look forward, I think that this study is important to us because it will help discharge another key uncertainty for the molecule, and that's whether the acute toxicity profile that we've seen in adults will be similar to what we observed in a pediatric population.

As I mentioned, all of our dose-limiting toxicities were hematologic in nature, and we know that, in other settings, children may have a more resilient hematopoietic system for hematologic toxicity. So based on the mechanism of this hematologic toxicity, it's possible that the

recommended phase 2 dose in a pediatric setting may be different than what we've observed in a monotherapy setting and may potentially even be higher.

In addition, while the PK data and the efficacy data that will be derived from the ongoing COG study are really the key inputs into our dose selection strategy, there are several parallel efforts that we're having to help further inform this strategy, the first of which is an ongoing C14 study in adult patients, where radio-labeled prexasertib is administered to help us characterize in the adult setting the clearance pathways.

At the current time, we do not have any drug-drug interaction limitations on concomitant medications in our ongoing adult studies. However, these data will help inform what we should be thinking about in the future and in particular as it relates to or lower age limit.

We know that CYP maturation is not complete in the youngest of patients, so in both the COG study as well as our proposed study, we proposed

excluding patients less than 1 year of age until data from this study are available to help us inform.

In addition, the C14 data will be important as we build a physiologic-based PK model to understand if there are other variables or factors that should be taken into account in our dose-selection strategy.

Another parallel effort that my colleagues in our PK and PD group have been working on is using our adult population-based PK model to scale and to extrapolate what the equivalent systemic exposure to the adult-recommended phase 2 dose would be in patients that have lower BSAs than what we've treated in our adult studies.

You can see the results here, and I think these results help confirm the appropriateness of the starting dose of 80 milligrams per meter squared in the Children's Oncology Group study. So all of these factors will come together to help inform our dosing strategy, and in particular, the pediatric recommended phase 2 dose.

So that's a summary of our ongoing and our completed work. But as we look forward, I think there's one final challenge that perhaps prexasertib has as we look to pediatric development. And that's whether the non-clinical data that we have, which we find compelling and exciting, will actually translate to the clinic.

We know from a historical perspective that not all data translates, and we also know that monotherapy data, in particular in a relapsed refractory setting, has not often been optimal.

So we want to minimize the number of patients that may be exposed to the agent if the data do not translate. But on the other hand, perhaps we have some cautious optimism that this agent may actually help translate, and then we may be able to have a practice-changing agent.

If that's the case, then we want to treat a sufficient number of patients to be able to characterize those effects and potentially be able to understand what signals of monotherapy we may have to both inform our monotherapy as well as

combination plans.

So we've tried to balance those two considerations as we've proposed our next study. This study would be a parallel cohort, independent cohorts of patients with relapsed refractory neuroblastoma or relapsed refractory rhabdomyosarcoma.

The age criteria would mirror that of the COG, and patients that are candidates for conventional therapy would be excluded. No more than 2 prior therapies would be allowed for the relapsed refractory setting, and the primary objective would be response rate.

Response rate would be used in an interim analysis that would occur after 20 patients to establish whether we have an initial signal. If more than 2 responses are observed, the study would be extended, or that particular arm would be extended to 55 patients. And this sample size would then allow the lower bound of the 95 percent confidence interval to exclude 15 percent, which we propose would suggest a clinically meaningful

improvement over standard-of-care options.

But we recognize that response rate in and of itself is probably not a sufficient measure of clinical benefit. Duration of response, event-free survival, and overall survival are all key secondary objectives to measure the duration and the extent of the response. In addition, we propose to include patient-focused outcomes, pharmacokinetics, and biomarkers as additional secondary endpoints.

With our understanding of the rarity of these patients, we recognize that a study of this size may need to be a global study that will leverage cooperative group involvement, and we appreciate the comments in the last session to provide some guidance on how we could approach that.

So in summary, for our prexasertib pediatric development plan, our adult data would suggest that the primary toxicity of this molecule is hematologic, reversible, transient, hematologic toxicity, and is suitable, the profile, for

evaluation in pediatric patients. We've extended our non-clinical data, where we've observed the strongest signal in neuroblastoma and rhabdomyosarcoma, but have observed signals of efficacy in other models of pediatric sarcoma.

Data from the ongoing phase 1 study will be critical to characterize the monotherapy toxicity in the recommended phase 2 dose that will inform a future study and our proposed study in relapsed refractory neuroblastoma or rhabdomyosarcoma.

We look forward to getting the committee's comments both on this design as well as other places we should consider giving the safety and efficacy profile of this drug for both a monotherapy as well as combination.

I thank you for your attention today, and we look forward to addressing any clarifying questions you may have.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you very much. We will now take clarifying questions for Eli Lilly. Please remember to state your name for the record

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

Elizabeth?

DR. RAETZ: Elizabeth Raetz, University of Utah. Thank you very much for the clear presentation. I might have missed it, but do you have particular assays that you use to look at the biological activity of the drug?

DR. LIN: If you could clarify in what nature of the biological activity are you most interested in?

DR. RAETZ: Just to see if you're effectively getting checkpoint inhibition, do you have any readouts that you would routinely look at?

DR. LIN: Yes, certainly. I think I'll ask my colleague, Dr. McNeely, from our oncology patient tailoring group, to talk about some of our non-clinical assessments that will address that question.

DR. MCNEELY: Sam McNeely, oncology patient tailoring. So in our pre-clinical models, most of the markers that we would use to assess whether or

not we're hitting the target would be phospho proteins that are reflective and have an activated DNA damage response, that being phosphor RPA, phospho CHK1, gamma-H2AX, which is a marker for DNA damage.

Clinically, we did assess some of those markers in our phase 1 study JTJA. We looked in circulating tumor cells as well as hair follicles for induction of gamma-H2AX. Unfortunately, we didn't see any statistically significant differences.

DR. RAETZ: Thank you. I have another question just as it pertains to the leukemia trial. So it sounds like there's an ongoing trial in adults with AML, with a combination of the agent with fludarabine and AraC. And I just wondered if there were any issues that you've seen to date with hematologic toxicity in that particular population?

DR. LIN: That study is an investigator-sponsored study that's being run by colleagues at MD Anderson. The study is ongoing, and data is not available. But at the current time, we haven't

seen anything that would continue to have us be interested in hematologic malignancies as a potential place setting for prexasertib.

DR. MASCARENHAS: Leo Mascarenhas, Children's Hospital, Los Angeles. Thank you for your clear presentation. I had some questions regarding your pre-clinical model. The dosing of prexasertib is very different from what is proposed in the clinical trial. How do you think that affects interpretation of the results, which you might have, and what bearing might it have?

I have several more, but that's the first question.

DR. LIN: Thank you. So yes. I think the schedule that we're using pre-clinically is a daily times 3 that's administered BID. And part of that is due to --

DR. MASCARENHAS: By which route? I'm sorry.

DR. LIN: I'm sorry. It's by subcutaneous, yes, subcutaneous route. And the pharmacokinetic and pharmacodynamic data that we've derived from

that model would suggest that differences to clearances in the rodent species, that that model is approximating the same exposure levels that we're achieving in the clinic.

Now, it may be a slightly different profile because of the daily times 3 dosing versus a single dose administered once every 2 weeks, but the exposures are comparable between the two schedules.

DR. MASCARENHAS: My second question is with regards to the neutropenia, which you've said is transient. But it looked like, at least in my interpretation of the graph, about 90 percent of patients experienced neutropenia, and in 70 percent of them, it was grade 4, which is severe.

The potential of combining that with cytotoxic chemotherapy, can you expand further on that?

DR. LIN: I think that that was one of the challenges that we faced, is how we do combine this. And so the agents in our adult setting that we're combining with are -- cisplatin is where we started, as well as with pemetrexed, as well as

5FU. And those agents, and particularly cisplatin, are not necessarily associated with the same level of neutropenia as some of the other agents. And we did that intentionally to cautiously understand what our ability to combine was.

At the current time, we are generating data. It seems as though there are differences between the cytotoxic agents, so cisplatin may be an agent that we can combine with. I'm not sure all cytotoxic agents we'll be able to combine with given the overlapping hematologic toxicity.

DR. MASCARENHAS: So that might have some relevance for the pediatric cancers, which you are proposing to develop this agent. And further, cisplatin is not generally used in the treatment of rhabdomyosarcoma and has limited utility in the treatment of neuroblastoma, though it's one of the drugs which is still used.

So really moving to your pediatric development plan, I have a clarification, and that is in the initial phase 1 of the phase 2 plan, you hope to enroll 20 patients on each cohort, and if

you have more than 2 responses, expand it to a further 35 patients, for a total of 55? Did I interpret that correctly?

DR. LIN: Correct, but each cohort would be independent; so yes.

DR. MASCARENHAS: Yes, so 55 in each and 20 in each.

DR. LIN: Correct.

DR. MASCARENHAS: So that's what I was clarifying. So that's a large number of patients and an expensive use of patients. I mean, these patients are rare. It's limited. And while you may get a stronger signal and increase the power and precision, the ultimate translation of the drug, that many patients may not be necessary, and a more accelerated definitive potential study might be desirable. A simple Simon 2-stage, 20 or 24 patients totally, might be able -- and if you see a good signal, could potentially allow you to advance this agent to a group of patients with a poor prognosis, either in the relapse setting or in the upfront metastatic setting, provided we have

data of combination together with cytotoxic therapy.

DR. LIN: Thank you for the comment, and I think that's part of what we were eager to hear from the committee, recommendations on that proposed design, so thank you.

DR. ARNDT: Carola Arndt, Mayo Clinic. Thank you also for a good presentation. Can you expand a little bit on why you're choosing in your proposed pediatric studies to limit to the rhabdo and neuroblastoma? One of your very early slides showed activity given in vitro in most of the other typical pediatric sarcomas.

DR. LIN: So our strongest signal was observed in neuroblastoma and rhabdomyosarcoma, so that was the area of focus until we could see that signal. But I think you've rightly outlined that we have seen activity in other tumor settings.

Perhaps I'll ask Dr. Stancato from our oncology patient tailoring group to come and expand a little bit on those data because I think we're excited about those and interested to see whether

we should consider those either in a separate study or in this study.

DR. STANCATO: Lou Stancato, oncology translational research. So we have seen activity in desmoplastic Moran cell tumor model, a patient-derived xenograft model. And in that model, the data were actually particularly striking in that once the tumor was essentially eliminated, we observed a complete response. It never came back.

So I understand the numbers of patients with DSRCT is very low, but it's a high unmet medical need. So that's an area that we are starting to expand additional pre-clinical evaluations. We're trying to find other desmoplastic Moran cell tumors. We're also expanding into NPNST to understand the potential activity of our molecule on the NPNST.

As far as the other sarcomas, I think we all know there's a translational gap, I think one could say, from cell-line work to in vivo work. With this molecule, however, for the most part, we see a pretty good translation from the cell line to the

in vivo when it comes to the soft tissue sarcomas.

When we start talking about the bony sarcomas so to speak, the Ewing sarcoma and osteo, there the translatability is not so high. But one thing I can share -- and these are data that have read out after the time that we submitted our documents -- is that we're starting to see activity say in osteosarcoma in combination with cisplatin, so with chemotherapy.

So in those other histologies, where maybe the translatability for a single-agent activity is not there, perhaps in combination, that's where the molecule will demonstrate its true capability.

DR. ARNDT: Also Ewing's or just osteo?

DR. STANCATO: Ewing's, thus far we have not done much in the combination setting in Ewing's. That is definitely a gap that we need to fill.

DR. ARNDT: So are there considerations for future to look at combination treatment in some of these tumor subtypes like osteosarcoma?

DR. STANCATO: Are we talking non-clinically or clinically?

DR. ARNDT: Yes.

DR. STANCATO: Certainly non-clinically, because I think it speaks to potentially two different mechanisms of the molecule, the single-agent activity and its ability to sense and respond to DNA damage. So I think it's incumbent upon us to really expand on that, those two different mechanisms, and see just how far this molecule can go, so to speak, across the pediatric landscape.

So those are ongoing. And I want to emphasize that with this molecule, we are highly engaged with the external community. We are working with people across the country and really in the E.U. to do the type of studies and experiments that you indicated.

DR. ROTH: Just to expand on that a little bit, my question was, I want to make sure I walk away with the right sense. So on paper, it looks like it's tabula rasa in terms of predictive markers.

DR. LIN: I think that we can classify markers of either increased replication stress or

DNA damage repair into broad buckets that may sensitize. Actually, having specific markers that we can do is still something we have to work on.

DR. ROTH: I meant more broadly. So pertaining to your development in the adult setting, you already have a basket trial in people with DDR deficiency and have a phase 2 in combination with a PARP. So that sends a strong message.

My most enthusiasm about a first-in-class molecule is the potential broadness of the effect, so that's why I was trying to get a sense of kind of at the next level, how you're going to cast the net, wide or narrow.

DR. LIN: Yes. It's a good question. I think those two studies in particular will help us inform whether there is specific populations. I will say pre-clinically, from what we've observed, both in non-clinical models as well as adult models, this molecule does have very broad activity, so we certainly don't want to narrow too soon and then miss out on some of those

opportunities.

So at the current point in time, apart from the basket study that you referenced, we don't have any inclusion criteria restrictions, and I think the retrospective analysis will help us understand if those are things we should put into place as we move forward.

DR. MacDONALD: Tobey MacDonald, Emory. The pediatric phase 1 includes CNS tumors. What pre-clinical data exists to justify inclusion of that group?

DR. LIN: So our ability to cross the blood-brain barrier is something that we have assessed in a non-clinical model with radiolabel. And with the C14 radiolabel in non-clinical models, we do not see strong blood-brain barrier penetrants in an intact blood-brain barrier.

However, I do think that the study that the COG has proposed will help provide some input as to whether that translates to clinically based on what they see with the patients that do have CNS involvement, but our non-clinical data right now

would suggest we may not have strong blood-brain barrier penetrants in an intact blood-brain barrier.

DR. MacDONALD: Are there any adult brain tumor ongoing studies that have shown any response?

DR. LIN: No. So we don't have any data or any studies ongoing right now in adult brain tumors.

DR. MacDONALD: Thank you.

DR. PAPPO: Alberto Pappos, St. Jude. I was just curious, on your dose-expansion cohorts, why did you pick these histologies that had carcinomas, the anal? Were they identified as sensitive in the phase 1, or did they have a unique characteristic, a specific mutational defect, P53 or ATR, that makes them particularly sensitive to this drug?

DR. LIN: So as you know, when you're in phase 1 development with a new agent, you kind of follow where your initial signals are. So in the dose-escalation portion of our phase 1, we had two partial responses. One was in a head and neck patient and one was in an anal cancer patient.

So that drove the opening of those two cohorts and some published literature at the time that suggested that squamous non-small-cell lung had a lot of genetic overlap with head and neck and may be an intriguing target as well.

For your question as to whether there's anything specific about those tumors that may drive it, I'm sure it's not lost on you that each of those are HPV tumors. And HPV itself, through E6 and E7 mechanisms, may deplete nucleotide pools just like MYC can result in increased replication stress.

So while that's an area of work that we still have ongoing, that would probably be perhaps one of the more strong tailoring hypotheses we'd have around those tumors.

DR. WEIGEL: Brenda Weigel, University of Minnesota. I'm wondering if you can expand a little bit more, both on the pre-clinical as well as the adult clinical trials in combination, because in just thinking about the mechanism of prexasertib, you're looking at combinations with

cytotoxics, some antibodies as well as small molecules. And I think probably the potential dosing sequencing mechanisms of action in those different settings might be very different.

What steps are you taking to try to optimize looking at maybe different classes of agents in combination with prexasertib and how we might appreciate the direction that that work is taking?

DR. LIN: Maybe I could speak first to the clinical efforts that we're doing, and then we'll turn to Dr. Stancato to talk about some of the pre-clinical efforts.

So from a clinical perspective, I think you rightly point out scheduling is a very important consideration and one across the field of DNA damage kinase that's being discussed.

In our ongoing phase 1 study with cisplatin, we're looking at two different schedules, so we administer both cisplatin and prexasertib on day 1 of each cycle, and then we also have another schedule where we're looking at cisplatin with prexasertib being administered 24 hours later to

try to potentiate some of that DNA damage.

Each of those schedules are tolerable, but they do have differences in their safety profile. And I think it's difficult to say in a phase 1 what the differences in the efficacy will be. But I think that you're exactly right, that scheduling is not a trivial consideration as we move forward into combination therapies.

To answer your question around kind of how we're approaching which combination therapies, I think some have been a bit of a practical element, as I alluded to with not wanting to pick agents that already themselves have very high levels of hematologic toxicity. But we know that the anti-metabolites from the literature as well as our own work are a very attractive combination partner.

Cisplatin was chosen because of its DNA cross-linking, a little different mechanism of action. And then pemetrexed I think is intriguing because, like some of the other anti-metabolites, it also can potentially deplete nucleotide pools and have a replication stress component to it. So

we have tried to think about how we can approach some of those targeted or cytotoxic combinations.

Then I think one of the really interesting few things over the field of CHK biology over the last several years is the interplay that it has with so many cell signaling pathways, whether it's the PI3 pathway or the MAPKAP pathway.

So I think some of the agents that then we've selected, in particular to look at, have tried to leverage some of the emerging data that those agents and those pathways may have both on DNA damage repair and that CHK may have on those pathways.

So as far as some of the specific combinations that we're looking at in our combination setting, I'll now have Dr. Stancato address that.

DR. STANCATO: Dr. Weigel, do you want me to explain some of the combination work that we've done? Is that part of your question?

DR. MacDONALD: If possible, because I think it gets back to a question Dr. Mascarenhas alluded

to. I think as we think about the pediatric tumors we potentially want to ultimately end up in, what data do we have from the adult sphere that will inform some of that combination, what pre-clinical data do we have? And how can we optimize that for the tumors of interest that we may want to take forward?

DR. STANCATO: Okay. So I'll tell you what I do know. What we know is that we have a molecule that has widespread single-agent activity, so we spend a lot of time fleshing that out and developing a robust data package as a single agent.

Now we're starting to look at tumors that either don't respond or perhaps that do respond, but then ultimately we see resistance arise. And that's starting to drive some of our combination studies.

So in particular, in rhabdomyosarcoma, we've looked at some of the standard of cares that you know so well, doxorubicin, irinotecan, cyclophosphamide. They all combine very well with the molecule. They all lead to a complete

regression of a couple of rhabdomyosarcoma models.

We're starting to look now at osteo, going back to the question I answered earlier, where the molecule is not quite as active as a single agent. In fact, it's simply not as active, across a limited subset, to be fair a limited subset, and we're looking at combinations of cisplatin and doxorubicin, and we're starting to see activity in combination with cisplatin.

So those are the standard-of-care combination studies that we've done. I had mentioned earlier, we want to circle back into Ewing's to do some more of that.

We've also done a limited evaluation of prexasertib with other targeted agents in the Lilly portfolio. These are data that are unpublished. They're preliminary. But we're going after the usual suspects that are involved with what's typically thought of as acquired resistance. We're seeing activation of map kinase pathway activation of AKT, et cetera. So we're making the rational combinations in that sense as well.

DR. MacDONALD: What about combination with radiation, since that would avoid some of your overlapping hematologic toxicity?

DR. LIN: Again, I think a combination with radiation is a very attractive combination. We have an ongoing phase 1 study in the adult setting in patients with locally advanced head and neck cancer, where we're combining with either cisplatin radiation or with cetuximab radiation to understand the tolerability of radiation.

I think, again, right now we haven't seen anything that would discourage us from considering to see how we could integrate radiation combinations into our clinical plan, whether they be both adult or pediatric.

DR. PAPPO: Any additional questions?

Thank you very much.

One more question, sorry.

DR. WEIGEL: With regards to the phase 2 plan, given limited numbers of patients on a phase 1, if there are potential responders on the phase 1 study, would that change some of your plan, or if

there were non-responders, significant non-responders, would that change some of your thoughts about next steps?

DR. LIN: Certainly one of the key secondary objectives of that ongoing phase 1 is to look at the efficacy, and we'd be remiss if we didn't take that into account as we moved forward. And I think you rightly say in both directions, if there's an enrichment of patients with neuroblastoma and rhabdomyosarcoma, and we don't see a translation at doses where we would predict efficacy, we'd have to reevaluate.

Conversely, if there were subtypes of patients that maybe we don't have as robust pre-clinical data for, we would certainly want to see how we could consider this.

Questions to the Committee and Discussion

DR. PAPPO: Thank you.

There is no open public hearing session in this portion of the meeting. We will now proceed with 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 question number 1.

DR. OSGOOD: Please consider the pre-clinical data and rationale for the development of prexasertib in neuroblastoma and rhabdomyosarcoma. Additionally, please discuss other tumor types that may benefit from the development of prexasertib.

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

DR. MASCARENHAS: I think I addressed this question with some of my clarifications earlier. I think the mainstay of treatment of rhabdomyosarcoma and neuroblastoma at this time is chemotherapy and radiation. So getting combination data or developing a plan with those drugs to incorporate chemotherapy or radiation together with this agent is desirable and should inform every potential clinical trial design.

I do think some of the other data is intriguing and needs to be explored, I think particularly in desmoplastic small round-cell tumor, which there is great need in that disease. It's a rare disease. And further exploring combinations in that, we do know that those patients transiently respond to alkylator therapy and camptothecins.

So combinations in that area, and further exploring that model, and screening the other available cell lines might be reasonable. And as Dr. Arndt suggested, I think further expansion to other sarcoma cohorts may be also reasonable.

Can I ask a panel member a question here to clarify?

Richard, any interest, just given the data of this agent together with pemetrexed, any of the anti-folds [ph] in osteosarcoma with this drug potentially? Can you comment on that?

DR. GORLICK: Diverging from the question you're asking me, it sounds like the most solid pre-clinical data is really in rhabdo and

neuroblastoma, and they are pursuing a path down the path where they have the most data.

So although you can always say it's interesting and you can combine the reality of it as their best signal, it's probably their best shot of activity. I think they're right in selecting neuroblastoma and rhabdo as the area of focus based on the data they have.

If you extrapolate to Ewing sarcoma, where it's almost like a BRCA mutant, that would be the reverse of where they're seeing activity. They're sort of like the BRCA positive types. So you would sort of move away from the areas where you're interested in PARP inhibitors.

Osteo is this genomically complex disease that, in terms of DNA damage repair, we don't really have any idea of what's going on there. I think it's nice that they're open to this down the road and that they'll explore combinations in vitro, which is the way to approach it. But I think they're right in that direction.

DR. ARNDT: I think it would be interesting

to get some additional data about the combination to see if the drug potentiates or acts synergistically with standard chemotherapy agents for osteosarcoma or Ewing's. So basically, I agree with what Dr. Gorlick and Mascarenhas have said.

DR. RAETZ: I was interested in the briefing document. It looks like there is some pre-clinical data that suggest that, perhaps, prexasertib would potentiate the activity of TKIs in pH-positive ALL. So I thought that was an interesting observation, and if that were pursued pre-clinically, certainly there's been a lot of, in the leukemia world, talk about Philadelphia-like chromosome ALL, too. So if you look in aggregate, that's now about 30 percent of the AYA population.

So pre-clinically, that might be a good population to look at further. I think one of the challenges would be the hematologic toxicity, so I was curious to see how the adult trial, how well tolerated the drug is with [indiscernible] being AraC. But if it proves to be safe, that might be an interesting population to pursue for the future.

DR. WEIGEL: I agree with what's been said. I think leveraging the strength of the pre-clinical data for neuroblastoma and rhabdomyosarcoma is the first step, while other areas are developed as spoken.

I was going to mention a similar thing to Elizabeth, because I wouldn't forget about the hematologic malignancies. I think there's a real opportunity there as well. And that in my mind is a separate development kind of strategy in a separate set of studies because I think the combinations and the populations are very different, and the toxicity issues may be very different. But I would certainly watch the adult data carefully and think about pre-clinical strategies there as well.

DR. PAPPO: I just wanted to add a small comment. Perhaps another combination that should be looked at and is active in actually both of these tumors and may not have additive hematologic toxicities increased in irinotecan -- and it sort of makes sense. Right? If you give the protracted

dose of irinotecan, your main side effect is diarrhea and not hematologic toxicity. Vincristine doesn't cause hematologic toxicity. And you're adding a trigger. Right?

Plug the spindle, get replication fork stalling, and then you go to the G2/M phase and add the CHK1 inhibitor is something to consider. And that may allow you to give this drug with some of the chemotherapies that are used in some of the sarcomas.

Any other? Greg?

DR. REAMAN: I would just like to go back to the hematologic development. I was impressed by the pH positive ALL findings as well. And although I clearly agree that they would be separate development programs from the phase 1 and beyond, I'm not sure that I would wait for adult data from the AML experience.

I think there's such an unmet need in pH-like ALL that this could be a real opportunity. So I would strongly suggest a sort of simultaneous development along those lines as well, should be

considered.

DR. PAPPO: Any additional questions or comments?

(No response.)

DR. PAPPO: So if I can summarize the comments from the panel for question number 1, we believe that these two histologics diagnoses are appropriate for further development of the drug based on the pre-clinical data. However, you need to pay significant attention to the combinations that you're going to be using, especially with the additive hematologic toxicity. Other subtypes that potentially could be explored would be desmoplastic Moran cell tumor and pH positive ALL.

We also strongly encourage you to strengthen your pre-clinical data with this agent on multiple other combinations. I mentioned vincristine and irinotecan, but other chemotherapeutic combinations.

I think that's it. Did I leave anything out?

(No response.)

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

DR. OSGOOD: Please consider the planned pediatric study of prexasertib in neuroblastoma and rhabdomyosarcoma and provide an opinion regarding the overall study design, including the patient population eligible for enrollment and the tumor types that are planned to be evaluated.

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

DR. WEIGEL: Brenda Weigel, University of Minnesota. So I do agree that these are the two patient populations based on the pre-clinical data, so certainly support that. I am concerned that for a single-agent study, it's a significant number of patients to commit.

I would encourage other study designs where if there is a very strong signal agent signal, we could do that with much fewer patients, and I think, still get to the same answer.

So I strongly support the evaluation of

these two patient populations, however, I would encourage a much smaller study.

DR. MELEMED: Can I get a clarification? Allen Melemed. I'm trying to get a clarification from FDA on what that would be because we would try to get a sufficient number that would be sufficient to show efficacy, and we thought 55 might be there.

What other kind of designs would you consider for a single-agent activity to make it smaller with the comments that Dr. Weigel had stated?

DR. REAMAN: I guess it depends somewhat on what you're going to do with the efficacy data that you generate. So if you're looking for a strong signal to continue development in that tumor, I think we've used -- or not from an FDA regulatory perspective, but from a general clinical trial and drug development perspective -- 10 percent, 20 percent response rates.

So I think I would throw the question back to you. What do you hope to see here? And depending on what you see, what would be your

plans?

DR. MELEMED: I will clarify. If we have response rates in the 15, 20 plus range, excluding the levels, we think that would be sufficient or potentially sufficient for activity or in efficacy in a pediatric population and potentially labeling for that.

DR. REAMAN: I think there are the kinds of activity signals, results that we've seen in the past that would at least suggest that there is activity, and adding more patients, and then it would also guide decisions about combination studies to really look for efficacy. So yes, I think 15, 20 percent would be very real.

Then I think, as has been pointed out, these patients are a scarce and precious resource. And although this is a very novel and exciting agent, I think the more we can do with the smallest number of patients, the better off we generally are.

DR. MELEMED: Thank you.

DR. MASCARENHAS: I just want to clarify something in terms of efficacy. I mean efficacy,

in terms of drug development, I think that's acceptable, but in rhabdomyosarcoma, we have no data to suggest that response rate correlates with outcomes.

So if you're looking at outcome as an indication, I don't think the study will answer that question with this number of patients for us to automatically prescribe this drug for patients with rhabdomyosarcoma or relapsed rhabdomyosarcoma.

DR. REAMAN: I don't think we're talking about automatically prescribing and approving. And that was my question back to Dr. Melemed.

DR. MELEMED: Let me just clarify. Drugs have been approved in the adult population based on response rate. And recently, in bladder cancer, with response rates as low as 13 percent response rates in hard-to-treat populations like bladder cancer, that has been approvals, accelerated approvals, for that population.

So we're trying to understand if you did see activity at that level, what FDA's perspective would be. It's not making people prescribe, but

having a drug that could be potentially available.

DR. REAMAN: Again, we could certainly put information in the labeling based on response rate. I think if we saw an incredible response rate in a relapsed refractory set of patients with single-agent therapy, that might be something to consider. But I think barring that, my understanding was this was really an attempt to evaluate and seek an activity signal that would influence further development.

DR. GORLICK: Richard Gorlick. In general, pediatric tumors are chemosensitive diseases where you see a response rate. The key issue is defining whether the response rate is sufficient to move it forward and do additional studies to clarify more precisely the level of activity.

The reason you use larger numbers of patients is to more precisely define a response rate. The way we achieve making our trials smaller is by looking for a greater effect size because unless the effect is sufficient, that its incorporation into an upfront therapy is likely to

change the outcome when combined with other agents that are chemosensitive. We're less interested in their further development.

So the key issue in defining sample size is really the effect size you're looking for and what that is relative to projected. If you look for drugs that in these diseases can achieve a response rate of 10 percent, there is actually cytotoxics, irinotecan, et cetera, that can do that, and it becomes uninteresting.

So we don't want to precisely define the outcome around that boundary. What you want to do is set your bar for clinical development at a level that will be interesting for further pursuit, and that's what defines your sample size.

DR. PAPPO: Any additional comments or questions?

DR. OSGOOD: I just had one comment that sort of goes away from sample size a little bit, but another interesting thing that could be done with this trial would be to add an additional cohort of multiple histologies in order to further

look at some of these histologies that have been discussed, the more rare ones like desmoplastic small round cell and things like that, just to see if you have any activity in those areas as well.

DR. PAPPO: Go ahead, Brenda.

DR. WEIGEL: Yes. I would just say, building off of Richard's point, I think that that's really the key concept, and that effect size is something that is a moving target, depending on what your ultimate plan and goal is. And that's why I said we'd have to really think through what the endpoints are and the next steps to really set that at a level that's meaningful.

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

(No response.)

DR. PAPPO: So if I can summarize the panel's discussion, we once again agree with the patient population. I'm sorry. Go ahead, Greg.

DR. REAMAN: So I think we're all basically saying the same thing here. But what would be a meaningful effect size? Can you see a meaningful

effect size with 10 patients expanded to 20 patients, or do you really have to go to 55 patients? So is a response rate of 15 percent, 20 percent, 25 percent, what --

DR. WEIGEL: Yes. And historically, in pediatric oncology, with traditional Simon 2-stage designs -- and I'll be very careful in that comment -- in the traditional Simon 2-stage design, it is defined as an effect size of 10 percent to go to the second stage and 20 percent at the end of the second stage to move forward. And that effect size is combined PR/CR rates and resist defined, and that's the classic benchmark.

Now, in certain disease groups, there have been re-analyses of some of this looking at different endpoints and different ways of looking at modified 2-stage designs or other endpoints. But traditionally, that's what we have looked at.

DR. MASCARENHAS: Given that's a challenge, outside further development and incorporation to other therapies as a single agent, what probably would also be more interesting is time to

progression, particularly in a cohort.

This may be challenging in a formal phase 2 study, where patients enter at different time points, but in a homogenous population, that effect size may be more clinically -- and I'm not speaking for neuroblastoma here, but for rhabdomyosarcoma, that may be more clinically relevant.

DR. PAPPO: Any additional comments or questions further?

(No response.)

DR. PAPPO: So if I can summarize the panel's discussion on question number 2, we agree that the patient population that you have identified is suitable to study this drug. We strongly encourage you to look at an alternative study design that does not use as many patients in order to maximize this patient population that is extremely rare.

In addition to that, you also need to consider what is the effect that you're looking for and if the right amount, the 10 to 20 percent is really what you're going to be happy with, or you

think we're going to need something more for this to move it forward, and also to consider time to progression as another endpoint, not a primary endpoint, but as another endpoint.

Did I leave anything out or does anybody want to add anything to this? Greg?

DR. REAMAN: I guess also, in line with time to progression, which is I think a little bit difficult in a heterogeneous group of patients, it would be not only response, but duration of response. So durability is important as well.

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

DR. OSGOOD: Please address the plans for administering prexasertib in combination with cytotoxic chemotherapy regimens. Please address plans for administering prexasertib in combination with other targeted therapies.

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

DR. MASCARENHAS: Leo Mascarenhas, Los

Angeles. I think the concern is neutropenia. I think in pediatrics, that's easily addressable with the use of growth factors, potentially, and with the timing of your agent.

The 2-week dosing may make it a little challenging for the long-acting growth factor, but potentially when you're combining with cytotoxic therapy, the nadir may be expanded and you might need to dose it every 3 weeks. And I don't know how that's going to affect the PK and efficacy, but that's something to be considered. But at least in pediatrics, I don't think that issue, unless it's prolonged cytopenia with growth factor, will be an issue.

DR. WEIGEL: I think the real challenge with this agent is that there may be very different strategies to combination depending on which agents you're looking at. So I would give very careful consideration to the prioritization in the tumor types that you're most interested in, particularly we've talked about neuroblastoma and rhabdomyosarcoma, of really interrogating the

combinations that are of most relevance to those tumor types in a prioritization and then continue to go down the list.

I do think, given the role that radiation therapy has in both of these tumor types, that that also needs to be considered a very important combination to consider and the timing of using the drug around radiation therapy, as it is a component of the treatment for both of those diseases.

DR. RAETZ: Just one thing that was brought up before, the sequence that Dr. Weigel mentioned, I think would be very important to see if truly giving it 24 hours prior to cytotoxic chemotherapy does lead to potentiation. I think it's a very interesting question and would be relevant in the leukemia population and probably others as well.

DR. PAPPO: Any additional comments or questions?

(No response.)

DR. PAPPO: So to summarize the panel's comments on this question, we're aware that neutropenia is very prevalent with the use of this

agent, however the use of growth factors may help mitigate this side effect. However, when you combine it with other chemotherapy, you may experience changes in the schedule, that you may have to be given this therapy, not because of this drug, but because of the other drugs that you are giving. So you need to take that into consideration as to how that would impact the activity of your agent.

In addition to that, we strongly recommend that you interrogate combination therapies that are particularly important to these two subgroups of tumors that you have identified, neuroblastoma and rhabdomyosarcoma, and also to investigate the rationale for the sequencing of this agent in patients with leukemia.

Anything else I left out?

(No response.)

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

DR. OSGOOD: Please comment on whether rhabdomyosarcoma should be considered one disease

or divided into two disease entities for embryonal and alveolar rhabdomyosarcoma, given the different pathology and clinical course of these tumors.

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

DR. ARNDT: In a perfect world, I think it would be ideal to divide them into two separate categories, but given all the challenges with patient numbers, I don't think that that would be realistic.

DR. MASCARENHAS: I agree with Dr. Arndt on rhabdomyosarcoma, but a strategy may be to potentially address this in the context of a larger population and include adults with the disease, and you might be able to get more patients on.

DR. PAPPO: I also agree with the previous comments, and I think also that the data that you have in the pre-clinical models is very limited to say that it's more active against alveolar versus embryonal. But I do agree that both groups should be put together and to encompass a large population

such as adults.

Any additional comments or suggestions, Brenda?

DR. WEIGEL: Just to build on that, I completely agree. I would initiate all the studies as a single cohort of rhabdomyosarcoma. And I think if the pre-clinical and clinical data drive a signal that there is a differential response, then I would ask that question later.

DR. PAPPO: Any additional questions or comments?

(No response.)

DR. PAPPO: So in order to summarize this question, I think the panel agrees that two cohorts should be put together, and you should just explore a single cohort in rhabdomyosarcoma. However, if you identify specific differential activities as the trial goes on, then you could potentially modify that. Anything else?

(No response.)

DR. PAPPO: We will now move to question number 5.

DR. OSGOOD: 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 of the question, we will now open the question to discussion. Carola and then Leo?

DR. ARNDT: I didn't really get the sense, or maybe I missed it from the presentation, about long-term toxicities of this agent. Can we ask the sponsor if there is any preliminary data?

DR. LIN: At the current time, we wouldn't have any specific concerns around long-term toxicities, but our data is obviously in an older adult population. And given the mechanism of action where we're disrupting DNA damage repair, we're inducing double-stranded DNA breaks and then inhibiting some of the replicative processes, that was I think the genesis of the question.

DR. ARNDT: I guess second malignancies would be a major concern to watch for. But again,

these patients, at least in the initial studies, are going to be relapsed patients, and there's not going to be the opportunity to watch for second malignancies in the initial cohorts.

DR. MASCARENHAS: To add to that, I concur with second malignancies, but I would add to that infertility. But again, it may not be able to be addressed in the population.

DR. ANGIOLILLO: Anne Angiolillo, D.C. Children's. Just as an extension, answering the question with another question, one wonders then with the DNA repair, if a certain cohort of patients should be excluded, Fanconi, Bloom syndrome, whatever, should these patients have a malignancy, just to think about that when you design the trial.

DR. GORLICK: The concern about following these toxicities and relapse has been addressed, but not mentioned is in newly diagnosed patients. All of the other therapies cause the same toxicity, so it's going to take a long time and a lot of patients to decipher this as different from the

baseline.

DR. PAPPO: Any additional comments or suggestions?

(No response.)

DR. PAPPO: So if I can summarize the panel discussion on this question and the sponsor's, there's really no information on long-term toxicity on these agents, but we also have to take into consideration that it's an older adult population. This is a younger population.

On the other hand, the initial studies are going to be conducted on patients with relapse disease, so it will be very unlikely that we will be able to see any secondary effects from these therapies, for example infertility of secondary malignancies. However, if you decide to do this in newly diagnosed patients, you should have a plan in place to monitor long-term toxicities of these agents.

Anything else I missed or anything else anybody would like to add?

(No response.)

Adjournment

DR. PAPPO: We will now adjourn the meeting. Panel members, please remember to drop off your name badge at the registration table on your way out so that they may be recycled. Thank you.

(Whereupon, at 11:45 a.m., the session was adjourned.)