FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE ONCOLOGIC DRUG ADVISORY COMMITTEE

Session 2

Thursday, November 19, 2015

8:01 a.m. to 10:12 a.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

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C O N T E N T S

P R O C E E D I N G S

(10:49 a.m.)

DR. PAPPO: Good morning. We will now proceed with Session 2, lenvatinib from Eisai. Dr. 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 Oncology Subcommittee of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws under 18 U.S.C. Section 208. Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts of interest when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

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 the purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony;

contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

This session's agenda involves information to gauge investigators' interests in exploring potential pediatric development plans for two products in various stages of the development for adult cancers. 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 lenvatinib sponsored by Eisai.

This is a particular matters meeting during which specific matters related to Eisai's product will be discussed. Based on the agenda for today's meeting and all financial interest reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in

connection with this meeting.

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

With respect to FDA's invited industry representative, we would like to disclose Dr. Phuong Khanh Morrow is participating in this meeting as a non-industry voting representative and 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 other financial relationships that they may have with the firm at issue. Thank you.

Announcement of Change to Participants

DR. PAPPO: For the record, Dr. Deborah Armstrong and Dr. Brenda Weigel have left the table for this 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 of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

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

Likewise, the FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking. We will now proceed with the sponsor's presentation.

Sponsor Presentation - Dimitris Voliotis

DR. VOLIOTIS: Good morning. Members of the Pediatric Oncology Drug Advisory Committee, FDA and guests, thank you for the opportunity to speak with you today. I am Dimitris Voliotis. I'm an adult medical oncologist by training, and I'm the head of oncology clinical research at Eisai.

Why are we here today? We're seeking a written request from the FDA for pediatric development of lenvatinib in the United States to help address important unmet needs in the treatment of pediatric cancers.

Why lenvatinib? Lenvatinib is a novel receptor tyrosine kinase inhibitor with potent

activity against both VEGF and FGF receptors. It was recently approved for the treatment of thyroid cancer in the United States, the European Union, and Japan.

What has drawn our interest and the interest of experts, including those from the Children's Oncology Group, is the impressive activity of lenvatinib in combination with everolimus in our recent randomized trial in advanced renal cell carcinoma.

We're here today to discuss the rationale for investigating lenvatinib in pediatric cancer and specifically the rationale for combining it with everolimus in this setting.

I'll start the presentation with a brief introduction to lenvatinib, including its mechanism of action and unique features. Next, I'll review the data from our adult clinical trial program including the pivotal trial in thyroid cancer and a study of the combination with everolimus in renal cell carcinoma.

Finally, I will discuss the rationale for

our pediatric program, share data from our ongoing pediatric study, and provide a preliminary outline of two proposed pediatric studies in collaboration with the Children's Oncology Group.

First, let me tell you about lenvatinib. Shown here are the MAP kinase and PI3 kinase mTOR pathways downstream of the vascular endothelial growth factor receptor and fibroblast growth factor receptors. Both of these pathways promote angiogenesis. Signaling through the FGF receptor has been implicated as an important mechanism of escape from VEGF receptor inhibition.

Lenvatinib is a multi-targeted receptor tyrosine kinase inhibitor with activity against both VEGF and FGF receptors. Therefore, it does block both pathways.

The in vitro inhibitor activity of lenvatinib against a variety of targets is shown here, and sorafenib is included as a representative comparator. As you can see, lenvatinib is much more potent than sorafenib against all four isoforms of the FGF receptor. Lenvatinib stands

out with this type of activity against both VEGF and FGF receptors in the nanomolar range.

This graph shows in vivo inhibition of the angiogenesis. The green bars are VEGF-driven angiogenesis and the purple bars are FGF-driven angiogenesis. As you can see, sorafenib significantly inhibits VEGF but not the FGF-driven angiogenesis compared with a control.

In contrast, lenvatinib effectively inhibits both VEGF- and FGF-driven angiogenesis at 10-fold lower dosages compared with sorafenib. This is consistent with the in vitro data.

We've conducted a rigorous nonclinical toxicology and safety pharmacology program, including a juvenile rat toxicology study, and our findings for lenvatinib are consistent with other VEGF receptor inhibitors.

Importantly, the toxicity profile observed in juvenile rats was similar to that observed in adult animals, although the onset of toxicity and mortality was observed earlier in juvenile rats compared with the adult animals. With regard to

clinical pharmacology, we've observed a linear PK profile with minimal accumulation at clinical relevant dosages.

Lenvatinib is extensively metabolized with a half-life of approximately 28 hours, and there are no clinically significant drug-drug interactions, food effects, or QTc prolongations in healthy volunteers.

In our adult clinical development program, we have treated more than 2,400 subjects with lenvatinib at this point. This program includes phase 2 monotherapy studies in a variety of different tumor types. We've also conducted a number of phase 1b and phase 2 studies combining lenvatinib with other targeted agents or with chemotherapy.

In particular, we have completed a study in renal cell carcinoma in combination with everolimus, and I will discuss that study in more detail later. Other supporting studies have examined bioavailability, QTc, and food effect.

Finally, we have conducted two large phase 3

trials. Study 303 is the pivotal phase 3 trial that served as the basis for approval in differentiated thyroid cancer, and we have an ongoing phase 3 study in hepatocellular carcinoma for which enrollment has just been completed, and we're expecting the data to mature at some point in 2016.

Now, I would like to review the data from our pivotal phase 3 trial that was the basis for approval in radioiodine refractory differentiated thyroid cancer, Study 303.

A total of 392 patients are randomized based on the certification factors and inclusion criteria shown here. Patients were randomized to treatment with either lenvatinib 24 milligram once daily or placebo until disease progression. The primary endpoint was progression free survival by independent assessment. Secondary endpoints included objective response rate and overall survival.

Treatment with lenvatinib significantly improved progression free survival with a hazard

ratio of 0.21 and a p-value of less than 0.001. Median PFS was 18.3 months in the lenvatinib arm compared with 3.6 months in the placebo arm.

Lenvatinib also significantly improved the overall response rate, which was 65 percent in the lenvatinib arm compared with only 2 percent in the placebo arm. Mostly, those were partial responses. It is, however, noteworthy that there were also 4 patients with a complete response in the lenvatinib arm and none in the placebo arm. Overall, survival was a key secondary endpoint.

Neither treatment group had reached the median at the time of this analysis. Please note that patients in the placebo arm were allowed to crossover to lenvatinib upon disease progression. So we prespecified an analysis adjusting for the effect of crossover, which is shown here. With this, we achieved a hazard ratio of 0.62 with a p-value of 0.051. Without adjustment for crossover, the hazard ratio is 0.73 with a statistically nonsignificant p-value.

This overview provides some perspective from

safety relative to exposure. As you might expect, the longer patients stay on treatment, the more likely they are to experience an adverse event. The median duration of treatment in the lenvatinib arm was 16 months as opposed to just 3.9 on placebo, and the safety data place for lenvatinib represents 270 patient-years of exposure versus only 65 with placebo.

Serious adverse events occurred in 53 percent of patients in the lenvatinib arm compared to 24 percent in the placebo arm. Fatal AEs occurred in approximately 8 and 5 percent respectively.

When we look at the rate of adverse events by duration of treatment, the rates between the two arms are fairly comparable. Adverse events leading to treatment discontinuation occurred in 18 percent of patients in the lenvatinib arm compared with 5 percent in the placebo arm. Adverse events leading to dose reductions and/or dose interruptions occurred in 90 percent of patients in the lenvatinib arm compared to 19 percent in the

placebo arm.

Taken together, these data illustrate that the incidence of adverse events in the lenvatinib arm is partly a consequence of the longer treatment duration due to the efficacy of the drug and dose modifications allowed patients to stay on treatment.

The most frequently reported treatment-emergent adverse events occurring in greater than 30 percent of patients are shown here by grade. Hypertension, diarrhea, fatigue, arthralgia, decreased appetite, and weight loss were the most frequently reported adverse events. This safety profile is consistent with other VEGF receptor inhibitors.

Now, I would like to briefly discuss the rationale for combining lenvatinib with everolimus. As I showed you earlier, lenvatinib inhibits both the MAP kinase and mTOR signaling pathways downstream of VEGF and FGF receptors; and the everolimus inhibits the mTOR pathway.

These two pathways exhibit crosstalk at the

level of S6 kinase and S6 shown in blue. Therefore, the combination of lenvatinib and everolimus should have additive or synergistic inhibitory effects on angiogenesis and tumor growth.

Based on this preclinical hypothesis and preliminary clinical data, we conducted a large randomized phase 2 trial, Study 205 in adult patients with renal cell carcinoma. Study 205 compared lenvatinib plus everolimus with either lenvatinib alone or everolimus alone in patients with unresectable advanced or metastatic disease that have progressed following one prior VEGF or VEGF receptor-targeted therapy.

The daily dose of lenvatinib in the combination arm was 18 milligram compared with 5 milligram of everolimus, whereas the control arm used a full approved dose for each drug.

The study completed enrollment in 2013 and the PFS endpoint was reached in June of 2014. The results of the primarily analysis were presented at ASCO in June of this year. The primary endpoint

was PFS by investigator assessment. Key secondary endpoints were overall survival and overall response rate.

The combination of lenvatinib plus everolimus significantly improved progression free survival compared with either agent alone, meaning PFS was 14.6 months in the combination arm compared with 7.4 months of lenvatinib monotherapy and 5.5 months with everolimus monotherapy.

Comparing the combination arm with everolimus monotherapy yielded a hazard ratio of 0.4 and a p-value of 0.0005. Comparing lenvatinib with everolimus monotherapy yielded a hazard ratio of 0.61 and a p-value of 0.048. These results were independently confirmed by a retrospective, blinded radiology review. This showed a 72 percent concordance rate between the independent and the investigator assessment.

The assessment of tumor response by the investigator demonstrated a 43-percent response rate with the combination compared with 27 percent for lenvatinib alone and only 6 percent with

everolimus alone. One patient in the combination arm had a complete response compared with none in either monotherapy arm.

Notably, the median duration of response in the combination arm was 13 months compared with approximately 8 months in both monotherapy arms. These results were also confirmed by independent radiologic review.

An updated analysis showed that median overall survival was 25.5 months for the combination compared with 19 months for lenvatinib monotherapy and about 15 months for everolimus monotherapy. Comparing the combination arm with everolimus monotherapy yielded a hazard ratio of 0.59, and comparing lenvatinib with everolimus monotherapy showed a hazard ratio of 0.75.

Regarding safety, the overall distribution of adverse events in the combination arm was similar to that of the two agents individually. Here, you can see all treatment-emergent adverse events occurring in at least 30 percent of patients, and the numbers are all percentages.

The incidence of grade 3 or 4 adverse events are broken out separately, and grade 4 events are shown in brackets. As you can see, there were very few grade 4 events. Among the most common AEs, only one patient in the lenvatinib monotherapy arm reported grade 3 hypercholesterolemia, which is the 2 percent in the brackets.

Some adverse events were more frequent in the combination arm compared with the individual monotherapy arms, but diarrhea was the only symptomatic adverse event that was higher in the combination arm than in either monotherapy arm.

Now that you've seen the data from our adult program, the question for this committee is why should we study lenvatinib in pediatric cancer? I would like to share the rationale for investigating lenvatinib in pediatric malignancies and an overview of our comprehensive pediatric development program.

First, there is a clear unmet need in childhood cancers. Although majority of patients are cured with conventional approaches, there's a

large subset of patients, particularly those with sarcoma, who do relapse and become refractory to conventional therapy. There has been limited improvement in treatment outcomes over the past two decades.

Second, lenvatinib inhibits both VEGF and FGF receptor activity, and we know that both are relevant targets in pediatric cancers, particularly in sarcoma. We also know, from the literature, that other RTK inhibitors have consistently demonstrated activity in preclinical models of pediatric solid tumors.

With regard to the combination of lenvatinib with everolimus in pediatric cancer, we know from the literature that mTOR inhibitors have also demonstrated activity in pediatric tumors including sarcoma. We know that VEGF and FGF signaling cooperates with mTOR-mediated regulation of cell growth to drive development of pediatric tumors.

Targeting both pathways at the same time is a very attractive strategy. The combination of VEGF and mTOR pathway inhibitors may abrogate

several alternative signaling pathways, and this approach has shown promise in preclinical solid tumor models. Finally, we've shown that this combination is active and has a manageable safety profile in adult RCC patients.

Today, we'll share preclinical data that support investigation of lenvatinib in pediatric cancer, including data suggesting that the combination of lenvatinib with everolimus may have greater activity than either agent alone in relevant tumor models. Taken together, all of this evidence provides a compelling rationale for investigating lenvatinib in pediatric cancer.

Regarding the activity of lenvatinib in pediatric cancer models, we have observed activity across a number of pediatric tumor types when lenvatinib was combined with chemotherapy agent typically used in such tumor types. For example, in 305 pediatric osteosarcoma models tested, the combination resulted in better tumor growth inhibition compared with chemotherapy alone.

The addition of lenvatinib to chemotherapy

was generally well-tolerated in these animals as determined by changes in body weight. The studies were conducted as part of our pediatric investigational plan in Europe.

We've also data from two human pediatric sarcoma xenograft models in which we tested the combination of lenvatinib and everolimus. On the left is the A-673 human sarcoma model, and on the right is the G-292 osteosarcoma line that has amplification of the FGF receptor.

As you can see, the combination of lenvatinib and everolimus, which is the purple curve at the bottom of the graph, demonstrated greater anti-tumor activity than either agent alone in these models. The between group differences were all statistically significant.

In addition to these models, we have developed a comprehensive preclinical investigation plan in collaboration with COG investigators. We plan to investigate the combination as well as the single agent in both patient-derived and cell line xenograft models.

We will investigate a wide variety of tumor types relevant for the pediatric studies as shown on this slide. We've already initiated those discussions and have commitments from investigators as noted.

Given the observed activity in these preclinical models and the compelling rationale for pediatric development that I just reviewed, we have initiated a pediatric development program as outlined here.

We're currently conducting a phase 1 single-agent dose finding study. Once that is completed and we have determined the recommended phase 2 dose, we plan to further investigate the anti-tumor activity of lenvatinib as monotherapy in combination with standard chemotherapy and in combination with everolimus.

The first phase of this program will be accomplished as part of our ongoing pediatric study, Study 207, being conducted in Europe in collaboration with ITCC. The second phase of this program will be accomplished in two proposed

studies with in collaboration with the Children's Oncology Group.

First, let me show you the design of the ongoing pediatric study known as 207 that was developed in collaboration with PITCO and ITCC to fulfill the requirements of our European PIP.

The first phase is a single-agent dose-finding study cohort in solid tumors using a continuous reassessment method. Starting dose of lenvatinib is 11 mg per square meter, which is 80 percent of the adult flat dose of 24 milligrams.

Once the recommended phase 2 dose is established, there will be two phase 2 single-agent cohorts in differentiated thyroid cancer and osteosarcoma. Concurrently, there will be a dose finding, and then phase 2 cohort investigating lenvatinib in combination with ifosfamide and etoposide in osteosarcoma.

This study is enrolling patients age 2 to less than 18 years of age. EMA granted a waiver for children less than 2 years of age based on the findings from the juvenile rat toxicology study.

Based on the findings from our juvenile rat toxicology study and the safety profile of lenvatinib in our adult program, we will be carefully monitoring bone growth, cardiovascular events, diarrhea, hypertension, proteinuria, and renal function as indicated.

The first patient was enrolled in December of 2014. As of November 9th, we have enrolled 15 patients and response data are available for the first 9. These include patients with a variety of sarcoma subtypes who are treated with 11, 14, and 17 mg per square meter. Currently, 8 patients are ongoing in cycles 1 through 6 and 7 patients have discontinued because of either radiographic or clinical disease progression.

Among the 9 available patients, 5 have stable diseases, their best overall response by MRI, and 1 patient with paraganglioma had a complete metabolic response after cycle 2.

Preliminary safety data are available for 13 patients. Reported adverse events were mostly grade 1 and 2, and there were no treatment-related

grade 3 or 4 adverse events.

Five patients experienced an SAE as shown here. As you can see, the majority of these events were related to disease progression with the exception of pneumonia in the patient with the undifferentiated sarcoma and a grade 4 colitis in the patient with Ewing sarcoma. However, those adverse events were not considered to be related to study drug by the investigators.

This is a draft study design for the two studies proposed in collaboration with the Children's Oncology Group. In the phase 1b study, in patients with recurrent or refractory solid tumors, including CNS tumors, the dose of lenvatinib will be escalated in combination with everolimus using a rolling 6 design. This will be followed by a phase 2 study in the tumor type shown here. The study will use a Simon 2-stage design.

In each tumor type, an initial cohort of patients will be enrolled, and if activity is demonstrated as evidenced by at least one objective response, an additional cohort will be added. The

study duration will be up to 24 months. The phase 2 study will also include a small descriptive cohort of 15 patients with thyroid cancer.

When our pediatric program is completed, we will have treated a total of up to 277 patients, including up to 69 patients with lenvatinib monotherapy in Study 207, up to 30 patients with lenvatinib plus chemotherapy again in Study 207, and up to 178 patients with lenvatinib plus everolimus in the proposed COG studies. The program will include up to 132 sarcoma patients and 145 patients with other solid tumors, including CNS malignancies and thyroid cancer.

The results from our pediatric development program as just discussed should be sufficient for a written request. This program will provide an adequate safety database, and there will be sufficient data to be included in the prescribing information. There will also be sufficient activity data to allow COG to determine if a phase 3 survival trial is warranted.

In summary, lenvatinib is a novel receptor

tyrosine kinase inhibitor that has demonstrated impressive efficacy and a manageable safety profile in our adult program. We've shown that lenvatinib can be safely combined with everolimus, and this combination has promising anti-tumor activity in patients with advanced renal cell carcinoma.

We've also observed preclinical activity in pediatric osteosarcoma and other sarcoma models. That preclinical activity and the compelling scientific rationale served as the basis for the current pediatric development program, which includes an ongoing pediatric study and two proposed studies in collaboration with COG. That program will provide sufficient data to support a written request.

We are, therefore, seeking a written request from the FDA for pediatric development of lenvatinib in the United States, and we're interested to hear the committee's thoughts on our proposed pediatric program. Thank you very much for your attention. We look forward to your questions.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you very much for your presentation. We will now take clarifying questions for the sponsor. Please remember to state your name for the record before you speak. And if you can, please direct questions to a specific presenter. Steve?

DR. DuBOIS: Steve DuBois. Thank you for that presentation. Did I see correctly a 7.7 percent fatal AE rate in the phase 3 thyroid cancer trial? That would be one question.

Then for the combination trial in renal cell carcinoma, two questions related to that. Do you think that there's a biomarker of response to the combination that might be relevant to incorporate into a pediatric trial?

Secondly, you showed that lower doses of both the everolimus and lenvatinib were used in combination compared with their single-agent full doses. What were the data leading to those doses?

DR. VOLIOTIS: Thank you. Let's start with the first question regarding the fatal adverse

events. We've collected the data on the fatal AEs from the study in differentiated thyroid cancer. Those individual adverse events are shown here.

We couldn't find a discernable pattern. As you can see here, the time point of occurrence of those fatal AEs ranges from 14 or 15 days after treatment initiation up to 460 days or 170, 140 days.

The causes for the fatalities are very different. It's very difficult for us to find any particular pattern other than describing it. The only thing that is to say is that this is a very heavily pretreated patient population obviously. So we don't see a particular pattern or anything that would lead us to a conclusion for the cause of these adverse events.

The second question was regarding the biomarkers. At least, in the adult program in the differentiated thyroid cancer study, we looked at a variety of biomarkers. We were really not able to see a particular difference for a number of factors.

I would like to invite Dr. Sachdev to comment on the particular findings that we had with FGF 23 levels. But in regard to other biomarkers like VGEF circulating type 2, we couldn't see a particular selection criteria that would enable us to target a subpopulation here.

DR. SACHDEV: Thank you, Dr. Voliotis. Pallavi Sachdev, Eisai. As Dr. Voliotis referred, in our adult RRDTC study, we did see substantial clinical benefit regardless of biomarker status. We evaluated a few genomic markers as well as proteomic markers, and irrespective of mutation or baseline levels of these markers, we saw substantial clinical benefit.

The data that I want to share with you here is knowing that FGF is a relevant target for lenvatinib, we evaluated the serum levels of FGF 23, which is a surrogate pharmacodynamic marker for FGF R1 inhibition. For this graph that you're seeing here, in lenvatinib-treated patients, we saw an increase in FGF 23 levels at day 15 as well as cycle 2 day 1, which is 29th day after treatment.

This suggests that we are targeting FGF receptor in vivo at physiological concentration. We do not believe, as of now, we have a predictive marker for patient selection. But in the proposed studies and on the ongoing studies, we are collecting archival samples as well as blood samples to do retrospective evaluation of these markers, and we hope to continue to evaluate these markers for predictive markers.

DR. PAPPO: Alberto Pappo. I had a couple of questions --

DR. VOLIOTIS: I'm sorry. There was a third question. You asked the question about the dose in the combination being lower, 18 and 5. This was simply the result of our dose escalation program. The study that I showed, the 205 study in renal cell, included a dose escalation for the combination, and we simply experienced DLTs at higher dosages. So the feasible dose for the combination is 18 milligram for lenvatinib and 5 for everolimus. That's what we then took forward in the phase 2 program.

DR. PAPPO: Alberto Pappo. I had a couple of quick questions. Going back to your survival curve on Study 303, the survival of these patients were only those patients that switched or that were crossed over to lenvatinib, or these are all patients?

DR. VOLIOTIS: This is intent to treat --

DR. PAPPO: All of them?

DR. VOLIOTIS: Yes.

DR. PAPPO: Okay. The other question I had for you is on the preclinical models where you did ifosfamide and etoposide with lenvatinib. Do you know what schedule of ifosfamide and etoposide was used? Was it the daily times five schedule that you regularly use to treat osteosarcoma or was this just one single dose habitual dose agent?

DR. VOLIOTIS: Dr. Bauer, could you comment on that?

DR. BAUER: Nancy Bauer, Eisai. The ifosfamide was dosed only on day 1 and the etoposide was dosed on days 2, 3 and 4 of the study. Lenvatinib was administered for 7

consecutive days, days 1 through 7.

DR. PAPPO: Then a couple of additional questions. Do you know if there's any effect of lenvatinib in wound healing? If you plan to use this eventually into some sarcomas that require surgery, is there a concern for wound healing?

DR. VOLIOTIS: This is an adverse event that has been looked at for many TKIs. We did look at impaired wound healing in the context of our studies, and this is the rate that we found.

You can see that we're really talking about single-digit numbers here. This includes not just patients from the renal cell cancer study but on the left side is all patients with differentiated thyroid cancer, including those from the phase 2 and the phase 3 programs that have received lenvatinib. And the wound healing that we saw is minimal, I would say.

DR. PAPPO: The final question is, are there any preclinical studies showing the brain penetration of this agent?

DR. VOLIOTIS: We have conducted preclinical

experiment with radiolabeled lenvatinib given as a mono-dose in animals, and we observed a penetration of about 14 percent, meaning that 14 percent of the plasma level was also detectable in the central nervous system. So there's a modest penetration of the drug across the intact blood-brain barrier.

DR. PAPPO: Thank you. Anne?

DR. ANGIOLILLO: Hi. Anne Angiolillo. Thank you for your fine presentation. I just have a few quick questions that have already been answered. You had mentioned the concerns for bone growth.

I was wondering two questions. Could you comment on any concerns for puberty? Second, the diarrhea in the 303, what type of management was needed? I'm sorry. And the third question, how was it supplied? Does it come in different formulations?

DR. VOLIOTIS: I'm sorry. Could you repeat the last question, please?

DR. ANGIOLILLO: Puberty, diarrhea, and then the drug formulation availabilities.

DR. VOLIOTIS: Let's start with the diarrhea first, please. The majority of patients that experienced diarrhea in our adult clinical program had diarrhea of grade 1 and 2. We, in fact, had only one patient who discontinued due to diarrhea in the adult program in the renal cell cancer study in the combination arm. We had no patient who discontinued in the renal cell cancer study.

These diarrheas obviously occurred, but it's very manageable and [indiscernible], and with the studies that we conducted, this was part of the dose management and adverse management plan. Diarrhea was included in the individualized dosing that we applied to patients once they experienced certain adverse events and part of the adverse events management profile.

About 46, 47 percent of all patients in the renal cell cancer and the thyroid cancer study received some form of antidiarrheal medication. Half of them had received loperamide. The other half received some other symptomatic treatment.

Again, it occurs but it's manageable, and we

are able to keep patients on drug long enough so that they can experience the therapeutic benefit. The plan obviously is that we would implement the same dose management and antidiarrheal symptomatic management also in the pediatric studies.

The last question was regarding the pediatric formulation, correct?

DR. ANGIOLILLO: Puberty and effect.

DR. VOLIOTIS: Puberty, in terms of?

DR. ANGIOLILLO: Any information on any effects on secondary sexual development.

DR. VOLIOTIS: We have information on bone growth, which is a particular thing that has to be looked at in growing kids and adolescents obviously. Bone growth is a target effect essentially like with any other TKIs.

It is a reversible effect, and we are planning to include a careful bone growth management including height management and X-rays in those children that are undergoing treatment in the studies that includes follow-up after the treatment has stopped.

In the animal experiments and the toxicology experiments that we had, this is, again, a reversible effect. With the adverse event management and follow-up program that we have implemented, we think we are going to be able to see whether that's going to be a long-term issue. But again, we don't think so based on the availability of the tox data.

DR. ANGIOLILLO: How about additional sexual development, breast, that type of thing, testes --

DR. VOLIOTIS: Dr. Bauer, could you comment on the toxicology findings in terms of --

DR. BAUER: Nancy Bauer, Eisai. In the juvenile animal studies, we did see some effects on secondary development. These were attributed primarily to the marked body weight effects that were observed in the study.

The high-dose animals had very marked body weight loss and decreased body weight gain. We believe that any of the secondary effects that were observed were a result of that effect. Again, most of the effects that we have seen were reversible

and the animals, their body weight, once they were taken off study, did recover to a significant extent.

DR. RAETZ: Elizabeth Raetz. I was just wondering if you comment further on your rationale for the inclusion of the high-grade glioma patients, and then a little bit about the schedule of how the combination with everolimus, how the medications will both be administered.

DR. VOLIOTIS: Taking your first question first, the including of patients with glioma, we do not have, at this point, preclinical data. We do have clinical data. So we conducted a phase 2 trial in adult patients with glioblastoma and malignant glioma, which included a randomization cohort against bevacizumab.

You can see here that in bevacizumab naïve GMB patients, we actually achieved a somewhat higher response rate compared to bevacizumab alone, also, some effect in high-grade glioma patients with an approximately 8-percent response rate.

Based on these clinical data, we think it is

appropriate enough to discuss with investigators to include also glioma patients in the pediatric protocol. This forms the basis for including those patients.

DR. RAETZ: Thank you.

DR. VOLIOTIS: And your second question?

DR. RAETZ: Just the other question is how are the medications both administered?

DR. VOLIOTIS: They're administered orally?

DR. RAETZ: And continuously for both?

DR. VOLIOTIS: Yes.

DR. RAETZ: Okay. Thank you.

DR. KIM: A quick question expanding on the combination of the everolimus -- I'm sorry; AeRang Kim from Children's National -- the combination of the two drugs together, were there pharmacokinetics done and were there any interactions between using the everolimus along with the lenvatinib?

Also, I noticed that there's a significant amount of dose reductions that were seen with the lenvatinib. Is there accumulative toxicity that ultimately required lower dosing?

DR. VOLIOTIS: In the combination trial, in the 205, the renal cell cancer trial, we did population PK analysis. There appears that there is about 18-20 percent, clinically probably not significant increase in AUC and Cmax for both drugs. We will include a detailed PK monitoring in the children's trial, in the trials that we plan to do with COG. At this point, this does not appear to be a problem.

The second question?

DR. KIM: I noticed that there were several dose reductions for patients that are on for prolonged time. Is there accumulative toxicity effect that you saw?

DR. VOLIOTIS: It's not so much accumulative toxicity but it's really important that we -- the patients are being monitored very closely for adverse events. You saw that adverse events that are occurring at a higher frequency. Any of these adverse events can lead to a necessity of a dose reduction.

We believe that we are able to really

individualize the dose for both the monotherapy and the combination by carefully monitoring those adverse events. So it's not so much accumulative toxicity; it's just the continuous monitoring of the adverse events. And once they achieve a certain grade, that would warrant a dose reduction that that is being done since the ultimate goal is really to keep the patients on the study drug or on the combination.

In both trials, we were able to do so very successfully so that patients actually experience also the therapeutic benefit of the drug. It works very well at this point.

DR. PAPPO: Greg?

DR. REAMAN: Could you just clarify the direct evidence that lenvatinib inhibits FGF as well as VEGF?

DR. VOLIOTIS: If you can go back to the slide from the main presentation, and I would also like to invite Dr. Sachdev to comment on that.

We have clear in vitro and in vivo evidence, as you can see here, that lenvatinib is a very

effective inhibitor of both VEGF and FGF receptor-driven angiogenesis, in vitro, the IC50 shown in the box here and then in vivo, based on the models that we conducted on the right side of this slide.

Dr. Sachdev, could you further comment on the preclinical data please?

DR. SACHDEV: Thank you, Dr. Voliotis. As Dr. Voliotis has reviewed with you, lenvatinib targets the FGF receptors, and this is the in vitro and in vivo data. We have also evaluated lenvatinib in a model where FGF R1 is an amplified.

If I may have NC-45, please?

(Pause.)

Dr. Voliotis reviewed with you in his main presentation that lenvatinib activity was evaluated in osteosarcoma model. One of the models that it was evaluated in is the G292-clone. This is an FGF R1-amplified osteosarcoma cell line. This is the in vitro antiproliferative and antitumor activity.

If we can go to CP-27. We evaluated that in

a xenograft tumor model, and there, we showed that both the single agent lenvatinib, as well as the combination showed activity with a combination showing enhanced activity more than either of the single agent alone. The combination showed enhanced activity.

So we believe we're targeting the receptor, and we do have in vivo data.

MS. HAYLOCK: Pam Haylock. Looking at the adverse effects, it seems like a lot of them are GI or metabolism-related. I wondered if those things have long-term effects or if those are also considered reversible.

DR. VOLIOTIS: From our toxicology experience, those are reversible, and they're also reversible in our hands in the clinical studies that we have conducted. Once the treatment is being adjusted, either dose interrupted or the dose is modified or it has to be interrupted, the diarrhea stops.

MS. HAYLOCK: But also there's weight decrease, constipation, vomiting, nausea, decreased

appetite, and diarrhea.

DR. VOLIOTIS: Those are reversible side effects, at least from a clinical perspective. Nothing in the toxicology data indicates that this would be different.

MS. HAYLOCK: Okay.

DR. DuBOIS: Steve DuBois. As a follow-up question to Dr. Reaman's question, in the clinic are patients developing hyperphosphatemia, which has been reported as a pharmacodynamic marker of FGF R-inhibition.

Unrelated to that question, I wonder if you might share some of what you are doing either with single-agent therapy or the combination with everolimus in adult sarcoma indications.

DR. VOLIOTIS: In terms of the adults sarcoma trial, let's start with that first, we have included a number of sarcoma patients in the adult program in the phase 1, 2 dose escalation. This is 7 patients in one trial, 17 patients in the other trial. If I could have that slide, please?

We saw mainly disease stabilization here.

We do not have a separate phase 2 trial at this point in adult sarcoma patients, so the data that we have from a clinical perspective comes from the dose escalation part. Again, it's altogether, 24 patients.

We looked at calcium and phosphate.

(Pause.)

DR. VOLIOTIS: We do not have a slide on that. We did not systematically look at this. We know this is a postulated effect of the drug. We observed similar instances of hypocalcemia and hypophosphatemia. But at this point, again, we do not have a systematic database. This will part of the trials going forward to look at this little more carefully.

At least as far as clinical side effects from a clinical perspective, this did not appear to be a major side effect. We did not pick it up in our adverse event monitoring profile in the studies. We will be looking at this a little more carefully going forward, including in the pediatric program.

MS. WEINER: Susan Weiner. My question really is a follow-up to an earlier one that has to do with the GI symptoms. Though the GI symptoms themselves may be reversible, I guess it would, from a family's perspective, really be worth looking at whether or not they affect growth rate and whether or not the growth rate itself is impaired.

DR. VOLIOTIS: Again, the growth rate, in the absence of having really comprehensive clinical data in children, I cannot comment on the growth rate. I can comment on the diarrhea incidences, and I'll show you a little more detail here so that you can see the diarrhea incidences that we had in the monotherapy and the combination program.

As already mentioned, diarrhea was mainly grade 1 and 2. We had much less grade 3 and 4 adverse events. This is the data set here from the monotherapy trial, and you can see here that we had in the monotherapy differentiated thyroid cancer trial, 9 percent grade 3 diarrhea.

As already mentioned, we did not have to

discontinue a single patient in the trial with monotherapy in thyroid cancer. Again, with the appropriate dose management, we are able to keep patients on study drug.

The same effect, we also saw in the combination trial in the renal cell cancer trial. We have about 19 percent, 20 percent grade 3 diarrhea, and only 1 patient had to be discontinued permanently. So with the appropriate dose management and symptomatic treatment and dose interruptions, once patients get back on drug, we're able to keep them on drug.

In terms of growth effects, what we looked at was body weight. When looking at body weight over the course of treatment in the thyroid cancer trial in the monotherapy trial, it was actually very stable. We couldn't see a major effect here in terms of how diarrhea impacted on body weight over the course of the treatment.

These are the data that we have that would correlate a GI symptom like diarrhea, for example, to something like body weight. It does not appear

to be, over the course of the trial, an effect that leads to a major deterioration in body weight.

DR. PAPPO: Alberto Pappo. I had another question. On the thyroid carcinoma trial, do you know which tumors responded? Do you know if they were type 4 BRAF or RET re-arrangements and is there a signal? Because pediatric thyroid cancer is different from adult thyroid cancer; they don't have BRAF mutations, they usually have RET re-arrangements; or is it just inhibits everything and everybody responds?

DR. VOLIOTIS: We did look at BRAF and NRAS, KRAS in the tumors. There was no particular difference when looking at those factors. Those are baseline archival tumor biopsies, so we do not have fresh biopsies from baseline of treatment. But in terms of what we had available from the phase 3 program, there was no difference.

DR. PAPPO: Mark?

DR. KIERAN: Mark Kieran, Dana-Farber. I'm still trying to get my head around exactly what the target is. It's a drug that seems to have multiple

targets simultaneously, and you've kind of isolated out FGF and VEGF as the primary targets.

But it's PDGF alpha, which is also present in a number of different tumor types, rat, et cetera. Actually, in the documentation, there were even more than were listed on the slide.

How does one really know what you're going after in terms of how one chooses intelligently the right patient to go on this trial?

DR. VOLIOTIS: Well, that's certainly the million-dollar question. It is definitely -- what we can say, as already shown in the previous slide, it's very effective in terms of inhibiting VEGF and FGF receptor-driven angiogenesis and tumor growth.

At this point, in the absence of a biomarker, we would simply go after tumor types where it has been shown that those kind of drugs have a particular effect; for example, thyroid cancer, renal cell carcinoma, and I already mentioned that we're looking into the phase 3 trial in hepatocellular carcinoma. These are tumor types that in the past with other drugs have shown to be

particularly good for isolating the effect here.

Again, we are going to further look into tumor types primarily rather than isolating individual patient populations across different tumor types. There is not very good biomarker for lenvatinib or any other TKI at this point, so it's really difficult to say.

We do think, however, that with the combination that we have, the enhanced efficacy with combining the TKI with the mTOR inhibitor, that we're also going to be able to look further into more tumor types.

So the short answer to your question is we will have to use purely clinical selection criteria.

DR. KIERAN: I'm somewhat surprised by the toxicity profile both of the drug and the combination. For example, the toxicity profiles that have been reported with other TKIs for VEGF inhibition have had very significant rates of severe hypertension, wound healing, diarrhea that really brought many of those studies to their

knees.

So I'm surprised that with such good VEGF inhibition, you compared it to sorafenib, which we could debate whether that's exactly what that drug is in anyway; if you compared it some of the more traditional targeted small molecule inhibitors of VEGF. I guess I'm surprised that you're not seeing the kinds of toxicities that one would expect for VEGF inhibition, which again raises the question about are we sure about the target?

The same would be true for everolimus. Most people would see a good 20, 25 percent of severe hypocholesterolemia just based on the genetic polymorphism associated with the use of that compound that you don't seem to be seeing in your cohort.

DR. VOLIOTIS: In the combination, we did see hypercholesterolemia in the 205 study when combining lenvatinib with everolimus, so we did see that.

In terms of how to really segregate, separate the different drugs by their adverse

events, I think at the end of the day, it really depends on the particular on-target profile. This is a unique drug in that it really targets VEGF and FGF in a particular way, in a way that other TKIs, like for example sorafenib, don't do.

We are very much convinced that the effect that we see that is VEGF and FGF-driven, the clinical effects that we see, whether it's renal cell carcinoma or differentiated thyroid cancer, are really also the preselected tumor types that we have seen a lot of activity with other TKIs. We do think with the data that we have looked better because this is a better inhibitor for both VEGF and FGF.

The spectrum of the adverse events -- going back to the very beginning of your question, the spectrum of the adverse events is relatively similar. We do see hypertension; we see diarrhea; we also see hand-foot skin syndrome.

The incidence for these particular adverse events is different across the different drugs. Sorafenib, for example, has much more hand-foot

skin reaction. This has to do with the way that the individual drugs target the particular pathways and the strength of the inhibition of the receptors.

They are targeting similar targets, similar receptors, but individually, there are differences between them. We think this is why they have, for individual adverse events, a slightly different profile. But if you look across the board, those are very much also the AEs that have been reported with other TKIs.

DR. KIERAN: One last question. The data that you showed for the adult gliomas, one of the questions about the VEGF inhibitors in the context of the CNS tumors is whether there really just antiedema agents and not antitumor agents at all. Do you know whether you believe any of this is actually antitumor or is this just a different type of steroid?

DR. VOLIOTIS: This is certainly not --

DR. KIERAN: Acting like a steroid.

DR. VOLIOTIS: Yes, I know what you mean.

We simply don't have data for that. I cannot speculate. I think we have seen clear evidence of efficacy. I think a 20-percent response rate in comparison with bevacizumab is a good starting point. I think that's good evidence, phase 2 evidence, to get going on that. I think from that perspective, the clinical data would clearly justify that.

In terms of what we will see in the preclinical experiments, you saw that we're trying to really conduct quite a number of preclinical experiments, including glioma, so we'll be able to hopefully see something better there. But right now, the database that we have is primarily clinical.

DR. DuBOIS: Steve DuBois. To follow on Dr. Kieran's question about toxicity, we've talked a lot about thyroid but more in the sense of thyroid carcinoma and efficacy. But often as a class effect, there's hypothyroidism, and that may be a little bit difficult to assess in your phase 3 randomized trial. But in other patient

populations, have you seen much hypothyroidism?

DR. VOLIOTIS: Yes, we did look at this, and we have the data available for you. Again, you will see that when comparing this with other drugs, this is very much in the range of what have been observed.

We had an incidence of hypothyroidism ranging from 5 percent in the DTC patients to 17 percent in the non-DTC monotherapy patients and up to 37 percent in the renal cell cancer population with the combination.

As you already mentioned, this is a known class effect. At this point, it's unclear what the mechanism of action is. It's likely also related to VEGF inhibition in terms of regression of thyroid capillaries.

But if we can have the overview, please, of the hypothyroidism with the other agents? Our drug, lenvatinib, is actually on the lower end of the scale, so there are other agents that have reported a frequency in incidence of up to 80 percent or even higher with hypothyroidism as

you can see here on this slide. So we're very much in range and actually, again, on the lower end of that scale.

DR. DuBOIS: Thank you.

DR. KIM: Just a quick question on the proposed pediatric drug study design. You mentioned a number of cohorts for the stage 2 design. Can you comment a little bit on what you're going to be looking in terms of outcome data for those patient populations? I think the objective response rate is pretty remarkable in your adult studies.

The second question is would there be any role for other soft tissue sarcomas, not including just rhabdos, as that pathway is important in several other pediatric type soft tissue sarcomas such as synovial aSPS and MPNSTs?

Thirdly, in the thyroid population, is there any role for other thyroid carcinomas such as papillary or medullary? It seems like some of the targets also inhibit those.

DR. VOLIOTIS: In terms of the design of the

phase 2 studies and the indication that you mentioned, this is the overview of the phase 2 plan that we have in the discussed pediatric 207 program.

The slide that you just showed; I'm sorry. The COG trial. So we're planning to include patients with osteosarcoma, patients with Ewing sarcoma or rhabdomyosarcoma, as well as high-grade glioma.

The design for the cohort for the phase 2 trial that we propose, again, is by cohorts. It is assignment stage 2 design, which means that we enroll approximately 10 patients. Once we see an objective response, we're going to enroll additional patients in the range of 10 to 15 patients again.

With this kind of design, we are able to detect a difference in response rate of about 20. So with 5 percent being the lower bond, we would be able to detect a 25 percent or higher response rate with a 90 percent power. The same is true for the other cohorts when using the endpoint of PFS rate

at 4 months.

In terms of other tumors that we'll be enrolling in the clinic, this is from the ongoing 207 study. And again as already shown in the presentation earlier, this is primarily going to be focusing on osteosarcoma, as well as DTC. Osteosarcoma is monotherapy as well as in combination with chemotherapy.

In terms of whether we saw the kind of responses that we saw in other tumor types within thyroid cancer, we have limited data in anaplastic thyroid cancer where the drug seems to be very active. We're currently running -- or we're working with investigators on investigator-initiated trial in anaplastic thyroid cancer.

In terms of activity in medullary thyroid cancer, we included a smaller number of patients, about 10, in the phase 2 studies, and we could not see their particular activity. We don't think that's going to be good target.

These are here the data from the phase 2 program where you see the different thyroid cancer

tumor types.

DR. PAPPO: One last question. Mark?

DR. KIERAN: I was struck by the absence of tumors that are known to be VEGF for which prognostic information is available, neuroblastoma being the classic example where you can actually predict outcome just based on the VEGF expression within the tumor diagnosis.

Is a tumor like neuroblastoma, which is one of the more common pediatric tumors, excluded because your preclinical data suggested it wasn't good or is there another reason?

DR. VOLIOTIS: This is, right now, just simply focusing on those where we have some knowledge about where we think there is either clinical or preclinical reason to believe that it would make sense.

But we're very happy to discuss with investigators with COG, potentially starting with preclinical evaluation. At this point, simply, we focused on the data that we had available where we could justify, either from a clinical or

preclinical perspective, to include them. Those, we don't have for neuroblastoma so it would be the subject of further clinical or preclinical investigation. We're certainly open to discuss those.

Questions to the Subcommittee and Discussion

DR. PAPPO: Thank you very much.

We're done with the questions. We're going to move on. We do not have any registrants for the open public hearing portion of this session, so we will proceed directly to the questions to the committee.

We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Now, Dr. Leigh Marcus will read the first question.

DR. MARCUS: Leigh Marcus. Given the juvenile animal toxicity studies, what specific

short-term on-therapy and long-term monitoring plan should be considered in trials incorporating lenvatinib?

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

MS. WEINER: This is Susan Weiner. I'm repeating my comment about monitoring growth rate over the long term if these are kids are surviving.

DR. PAPPO: Steve?

DR. DuBOIS: Steve DuBois. I had asked my question about the rates of thyroid toxicity specifically because the safety monitoring slide for the pediatric program did not include thyroid monitoring, which I think would be really essential.

The other toxicity that's been seen relatively early after initiation of anti-VEGF R2 TKIs in the pediatric population have been decreases in the left ventricular ejection fraction. I note that the initial post-therapy echocardiogram takes place only after 16 weeks,

which may be a little bit long before looking at the first echocardiogram post initiation of therapy.

DR. PAPPO: With regards to the safety monitoring in the pediatric program, there is a slide that includes all of the safety parameters that are going to be included. Does the panel feel comfortable monitoring bone growth exclusively with X-rays?

There's some data to suggest that the changes are much earlier, and you can visualize them with MRI, although I don't know what the significance of that is. But does the panel feel comfortable just using X-ray or do you think we need to do something else?

MS. HAYLOCK: Pam Haylock. I think it's bigger than just bone changes and bone growth. It just seems like there's some metabolic things that happen, especially with the appearance. I think proteinuria was mentioned in one thing, and you brought up the issue of wound healing. It seems like there's something that's happening with

ingestion, so I don't know if it's nutritional.

The other point that I keep thinking about, at least in the adult population, weight loss is a significant poor prognostic factor. I don't know what the degree of weight loss is in this that's important. In a small child, weight loss of a few pounds could be significant.

DR. KIERAN: I think you raised exactly kind of one of the important issues. Most of those side effects are minor side effects that are probably associated with VEGF on target, certainly the effects on thyroids, certainly the nausea, the diarrhea, the weight loss, that kind of stuff. The bone growth is a good question.

Again, I don't think we have enough data yet in pediatrics to really understand this, and obviously it's something that hasn't been well-studied in adults although the preclinical models have shown that most of the changes that you see are reversible.

You tend to pick them up not on X-ray; you do tend to pick them up on MRI scan, so it's a good

point in terms of it would be good for us to better understand the process if you had an MRI of a growth plate as really the form of analysis for this.

DR. KIM: For many of our other phase 1 TKI inhibitor studies that have VEGF inhibition, I think the difficulty with proposing MRIs have been cost and also for many of our young children that are the ones that require it that have open grown plates, the addition of required sedation on top of that. I think if there were changes --

Many of the studies, what we've done is looking at X-rays, and if there are changes present, then going on to further evaluations with MRIs. One of the other problems with a lot of the phase 1 therapies is that the patients have not enrolled in long enough to really follow a long-term follow-up in terms of bone growth.

So it would be interesting in looking at some of the other diseases where patients have received TKIs for much longer to see what the long-term outcome would be on bone growth for young

patients.

DR. REAMAN: I was basically going to say the same thing or similar, that these reversible changes seen in the preclinical studies are reversible because the drug has been discontinued. But if we envision that this is going to demonstrate activity, then we assume patients are going to be on this for a much longer period of time.

I think whatever monitoring is conceived of is something that is both -- have to look at the short-term monitoring as well as long-term monitoring, and particularly for bone growth abnormalities.

DR. ANGIOLILLO: Anne Angiolillo. Just to add to that, I think in the adolescent or prepubescent following of the whole hypothalamic pituitary access with the secondary sex characteristics and those hormones, just to consider a testing along with thyroid.

DR. PAPPO: If I can summarize -- I'm sorry. Susan goes next.

MS. WEINER: Susan Weiner. One more comment, and that is since these are recurrent or refractory patients and they're heterogeneous with respect to diagnosis, it would seem to me that keeping track of their prior history, in particular whether or not includes RT for the cancer site, would be important because there may be interactions between the prior cancer treatment and the current regimen that's being investigated.

DR. PAPPO: Any additional comments?

(No response.)

DR. PAPPO: If I can summarize, the panel is interested in being sure that the company considers monitoring of the growth rate in the long term in patients that enroll in the study, to monitor for thyroid toxicity, to be sure to include the evaluation of left ventricular function a little bit earlier than, I believe it was, week 16.

There are concerns about proteinuria, wound healing, and weight loss, and we recommend that they are monitored closely. The issue of using MRI to evaluate growth plates was brought up. I don't

think there was a consensus, but it's something that perhaps could be considered.

In adolescents, to be sure to include markers not only for thyroid function but for sexual development, and then also to incorporate into the history of patients that are included in the study, track back what prior therapy they'd received, specifically radiotherapy, to try to identify some potential interactions with this thyroid kinase inhibitor.

Did I summarize everything okay or did I miss anything?

(Affirmative nods from the committee.)

DR. PAPPO: Okay. We will now proceed to the second question, and Leigh will read it.

DR. MARCUS: Leigh Marcus. Given the observed synergy with lenvatinib and the mTOR AKT pathway inhibition, please comment if there are other possible synergistic combinations of targeted agent or specific pathway inhibition that should be evaluated as potentially relevant in pediatric cancers.

DR. PAPPO: Comments? Steve?

DR. DuBOIS: Steve DuBois. I'm always a champion for IGF 1R inhibition in pediatric sarcomas, so thinking about combination approach with IGF 1R, either monoclonal antibody or small molecular inhibitor may be worth consideration.

DR. KIERAN: There's a lot of adult kind of data, some of it conflicting, so I'm not sure it's a specific recommendation. But sometimes it's a good idea to inhibit two parallel pathways to prevent escape, sometimes because your first drug never inhibits completely, adding a second inhibitor into the pathway.

A MEK inhibitor in this case might be the obvious choice to see whether or not you can really kind of shut down that signaling cascade and would at least be probably worthy in the preclinical models to maybe address some of those to see whether that's an appropriate to go forward as well.

DR. PAPPO: So as far as additional combinations that perhaps could be studied or

should be proposed in combination with lenvatinib would be inhibition of the IGF 1R pathway, either through a monoclonal antibody or a small molecule, and also consider MEK inhibition.

DR. DuBOIS: To clarify, I wasn't proposing that necessarily for the clinic for preclinical --

DR. PAPPO: Preclinical studies?

DR. DuBOIS: Preclinical evaluation in pediatric-relevant tumors.

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

DR. MARCUS: Leigh Marcus. Please discuss the need for pediatric-appropriate oral formulation of lenvatinib and a reasonable timeline and potential obstacles with development.

DR. RAETZ: This is Elizabeth Raetz. One of the concerns is with all the GI toxicity, I don't know what pediatric formulation is envisioned, but it may be very difficult for children to tolerate if they already have a lot of poor appetite, nausea, vomiting, diarrhea. So that may be a consideration.

DR. REAMAN: I think the other issue is that is currently a capsule formulation, which is going to preclude its use in children probably under the age of 6. Are there plans to actually develop a solution? There are, I assume. And are there food effects that really need to be evaluated with a different formulation that might be used in the studies?

DR. PAPPO: Any other comments or questions?

(No response.)

DR. PAPPO: I think regarding question number 3, one of the considerations should be that potential GI toxicity of this drug when a pediatric formulation is developed, given the fact that there can be other concomitant or comorbidities such as poor appetite and decreased weight gain or weight loss.

The second one is the current way that this drug is available is through capsule; so I think it's a 24-milligram or a 10-milligram, and are there any plans to develop a solution. We assume that there are; and also to study food effects when

this formulation is given to younger patients.

We will now go to the -- I'm sorry. There's one more thing.

DR. MORROW: PK. I just wanted to comment. I think that the company had looked at dissolving the capsule on apple juice, and it worked okay with children -- or with adults.

DR. PAPPO: Okay. So that's already been looked at, okay. They're going to have to develop a specific dosing based on surface area or anything, but they're going to have to figure that out.

For the final question -- Greg, has more questions --

DR. REAMAN: I think one other thing is since there is such a high incidence of GI problems, making sure that whatever oral solution is used doesn't adhere to NG tubes and interfere with bioavailability. Again, in younger children, that's something that will require evaluation, preferably in healthy adults first, of course.

DR. PAPPO: We will now move to the last

question.

DR. MARCUS: Leigh Marcus. I think Dr. Kieran talked a little bit about this, but we can open it up again. Please discuss the importance of evaluation of the CNS pharmacology of lenvatinib and the consideration of its assessment in primary CNS tumors.

DR. PAPPO: If there are no questions or comments concerning the wording or the question, we will now open this question for discussion. Mark, you're the obvious --

DR. KIERAN: I mean obviously, one of the issues in the VEGF inhibition is it's not clear that you need to penetrate the CNS obviously because you might argue that the target is actually -- if it's on the luminal side, then it already has access just by being in the bloodstream. Whether that's accurate in many studies that have looked at VEGF expression of particularly adult gliomas, where it was mostly done, sometimes the VEGF is on the abluminal, not on the luminal side, so that may not be absolutely

true.

You do have some data. I think you showed 14 percent relative to serum. You didn't say whether or not, for example, those brains had had all of the blood removed, so that it was true CNS -- parenchymal penetration as opposed to just there's a whole bunch of blood in the brain and that that accounts for the 14 percent.

So it would be important to know those things. But to some extent, your preclinical model should be able to answer this question, and I think that's what will drive the direction forward.

DR. PAPPO: Any concerns as far as enrolling glioma patients in the study without having adequate preclinical data or extensive preclinical data?

DR. KIERAN: It was fascinating that you did an adult trial, but you don't have any preclinical data for gliomas. Clearly, something led you down that pathway. Again, I'm still a little confused about exactly what the target is given all -- we know PDGF alpha, for example.

PDGF alpha is a critical component of the parasites in the central nervous system, and this has good activity against that target. That's why I wouldn't base it all on just VEGF.

Whether or not the VEGF effect is really related to antiedema and not anti-tumor, but you may have other components that actually are anti-tumor -- the fact that you're starting to see some responses in adults, and if that program continues to move forward and you can show those -- obviously, human beings are the best animal model we've got. And given how poor the prognosis is, I find the animal models, particularly the orthotropic ones where you are basically cutting open the brains, sticking in cells, there's breakdown of all of the normal stuff. It would be very hard to predict based on those kinds of experiments as the sole determinant of going forward. So I think your human data is almost the strongest component of that part of the rationale.

DR. PAPPO: Any other comments about

question number 4?

(No response.)

DR. PAPPO: So if I can summarize this, I think that the panel would be very interested in additional preclinical studies better elucidating the CNS penetration and how you measure CNS penetration using this drug. Anything else? Maybe look at PDGFR inhibition or no?

DR. KIERAN: No. I forgot when I looked at the original document, there were like 20 plus potential targets, and you can't separate them all or analyze them all. And to some extent, I don't think that's going to be the determinant of activity anyway, so I wouldn't say that should be required.

DR. PAPPO: Okay. Any additional comments or questions, even back to question number 1, 2, 3 or 4?

(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, and thank you very much for attending this meeting.

(Whereupon, at 12:15 p.m., Session 2 of the meeting was adjourned.)