FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

Topic 3

Wednesday, June 21, 2017

1:10 p.m. to 2:25 p.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

(1:10 p.m.)

DR. PAPPO: Good afternoon. We're going to get started. We will now proceed with topic 3, ASP2215, gilteritinib, from Astellas Pharma Global Development, Incorporated. Dr. Lauren Tesh will read the conflict of interest statement for this session.

Conflict of Interest Statement

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

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

The following information on the status of this committee's compliance with the federal ethics

and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with 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 interests of the regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meetings, members and temporary voting members of the committee have been screened for potential financial conflicts of interest of their own, as

well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers.

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

This session's agenda involves information to gauge investigator interest in exploring potential pediatric development plans for three 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 the 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 ASP2215, gilteritinib, presentation by

Astellas Pharma Global Development, Inc. This is a particular matters meeting during which specific matters related to Astellas Pharma's product will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Carola Arndt.

Dr. Arndt's waiver involves her stockholding in a potentially competing firm. The waiver allows this individual to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on the FDA's website.

Copies of the waiver may also be obtained by submitting written requests to the agency's Freedom of Information Division, 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 members and temporary voting members to

disclose any public statements that they may have had concerning the product at issue.

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

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

FDA encourages all 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 of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests 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 Astellas Pharmaceutical's presentation.

Industry Presentation – Andrew Krivoshik

DR. KRIVOSHIK: Thank you. Good afternoon. My name is Andrew Krivoshik, and I'm the vice president of medical oncology sciences at Astellas Pharma. Prior to entering the pharmaceutical industry, I received my clinical training in pediatric and adolescent medicine and pediatric hematology oncology.

I'd like to thank the FDA and the panel for the opportunity to present today. We are committed to developing gilteritinib as a treatment for children with AML and look forward to your feedback.

We are here today because of the substantial unmet medical need for pediatric treatment options in a particularly rare and deadly form of AML, FLT3/ITD mutated disease.

Gilteritinib is a targeted therapy currently in development for the treatment of FLT3-positive AML and has demonstrated significant, durable anti-

leukemic activity and appears well tolerated in adults with FLT3-mutated AML. The goal of our proposed pediatric program is to provide sufficient data for a label to inform prescribers.

Our proposed pediatric study population is based on our understanding of gilteritinib's mechanism of action as a FLT3 inhibitor and also where we see the greatest potential for clinical benefit. In light of those two factors, we limited the population to children with FLT3-mutated AML.

Our proposed pediatric indication is for the treatment of pediatric patients with newly diagnosed or relapsed refractory FLT3-ITD mutation-positive AML.

I will describe the disease and the need in our target patient population, gilteritinib's mechanism of action, and finally our proposed pediatric development plan.

Now, the disease description and unmet need. AML is a rare, rapidly progressing, and life-threatening cancer of the blood and bone marrow, characterized by proliferation of malignant

progenitor cells. When untreated or refractory, AML is often accompanied by severe neutropenia and/or thrombocytopenia and can be rapidly fatal. Even though most newly diagnosed patients do achieve an initial remission, relapse is unfortunately common.

In patients with FLT3-ITD mutated AML, only 21 percent achieve remission after salvage therapy. The median overall survival is 4.3 months after first relapse and less than 8 weeks after the second.

Although only 10 to 20 percent of pediatric patients with AML are FLT3-ITD mutation positive, outcomes are especially poor for these children. While 65 percent of all children with AML are alive at 5 years, only 20 to 30 percent of those with FLT3-ITD mutation live for 5 years. There is no approved targeted therapy for this rare disease in children. In fact, current clinical practice guidelines recommend a clinical trial with a FLT3-targeted therapy. This stands in stark contrast to the progress made to date in pediatric acute

lymphocytic leukemia.

To summarize, FLT3-ITD mutated AML is a very rare pediatric cancer with extremely poor outcomes and an urgent need for new treatment options.

I will now describe gilteritinib's mechanism of action. Gilteritinib is a potent, novel, oral targeted therapy that inhibits several tyrosine kinases with high affinity, most notably FLT3, which is the primary driver for gilteritinib's anti-leukemic effect. Importantly, gilteritinib has relatively low affinity for the off-target kinase c-KIT, which often drives hematologic toxicities.

Turning now to our adult development program, looking first at exposure, as of April, there are 16 completed or ongoing clinical trials, 179 volunteers, and 574 patients have received at least one dose of gilteritinib.

We will present data on 252 patients from study 0101. This is a first-in-human monotherapy dose escalation study in adult patients with relapsed or refractory AML. Gilteritinib doses

from 20 to 450 milligrams were explored in a 3-plus-3 dose escalation design. The maximum tolerated dose was 300 milligrams per day.

Although all cohorts of 300 milligrams and lower were expanded, based on anti-leukemic activity observed in doses 120 and 200 milligrams, these specific cohorts were further expanded to include additional patients with FLT3 mutated AML.

Looking at demographics, median age was 62 years and 51 percent were male. 76 percent had FLT3-mutated AML, and 64 percent had FLT3-ITD mutated AML. The majority had at least 2 previous therapies and a third had a stem cell transplant. A quarter had already received a TKI, mostly sorafenib.

Turning now to patient disposition, the most common reasons for discontinuation were disease progression and lack of response. 14 percent underwent transplant, and a third of those resumed gilteritinib treatment. Gilteritinib exhibited linear and dose-proportional pharmacokinetics at doses ranging from 20 to 450 milligrams.

Median t-max was between 2 and 6 hours following single and multiple doses. The estimated half-life ranged from 45 to 159 hours. Steady state was achieved by day 15.

Although in patients with wild-type FLT3 AML, the CRc rate was only 9 percent. High anti-leukemic activity was noted in patients with FLT3-mutated AML at 37 percent across all doses.

For patients with FLT3-positive AML on doses 80 milligrams or above, the CRc rate was 41 percent. Recall historical CRc rate in FLT3-ITD mutated patients is approximately 21 percent. The median overall survival of 7.1 months compares favorably to the historical survival of 1.5 to 4.3 months.

Importantly, the majority of the patients treated with gilteritinib were heavily pre-treated. Survival probabilities were 57 percent at 26 weeks and 22 percent at one year. Of particular note, currently 9 patients remain on study drug with the longest on for 3 years.

We also looked at molecular response in

patients with FLT3-ITD mutated AML to evaluate the quality of the response.

An 80-patient subset of the FLT3-ITD population treated with 120 or 200 milligrams of gilteritinib was analyzed. Molecular response was defined as a FLT3-ITD to total FLT3 ratio of less than or equal to 10 to the minus 2. 25 percent of the patients achieved a molecular response.

These patients had almost double the length of median overall survival as patients who did not achieve molecular response. In addition, 16 percent of the patients had a deeper molecular response. They were minimal residual disease, MRD negative. These data suggest that gilteritinib can induce deep molecular responses as a single agent in heavily pre-treated patients with relapsed refractory AML.

Looking at safety, overall gilteritinib appears well tolerated in adult patients with AML. Here are adverse events that emerge on treatment in at least 20 percent of patients, many of which may be associated with their underlying AML.

The most common drug-related adverse events were diarrhea, fatigue, and elevated AST. The majority were grade 1 or 2. The most common AE leading to discontinuation was AML or disease progression at 6 percent followed by sepsis at 2.8 percent and respiratory failure at 1.6 percent.

The most commonly reported AE leading to death was disease progression followed by multiple organ failure, sepsis, and respiratory failure. Of the 95 deaths, 7 were assessed as possibly related to gilteritinib.

I'll now discuss four key safety issues with gilteritinib treatment. Two patients developed posterior reversible encephalopathy syndrome, PRES, in study 0101. Symptoms included seizure and altered mental status. Both cases were confirmed by MRI. Gilteritinib was discontinued and altered mental status returned to baseline with no subsequent episodes of seizure.

An additional case of PRES was reported during compassionate use and was attributed to intrathecal cytarabine. Gilteritinib was restarted

without recurrence of symptoms.

Moving now to our electrocardiographic analysis, a concentration-related mean increase in delta QTcFF was observed. As modeling predicted this to be less than 10 milliseconds, clinically relevant QTc prolongation with gilteritinib is not anticipated. Ten percent of patients had a maximum post-baseline QTc interval greater than 480 milliseconds.

The majority of these patients were concurrently taking at least one concomitant medication with a known risk of QTc prolongation. No cases of Torsade de pointes were reported. Relevant exclusion criteria and electrocardiogram assessments are reflected in our protocols.

Moving now to creatine kinase analysis, an exposure-related association between gilteritinib and CK was observed. However, almost all of the observed elevations in CK were grade 1 or grade 2 and asymptomatic.

The reported incidence of drug-related grade 3 adverse events was low at 2.4 percent. Only

2 percent had drug-related SAEs. One patient on 300 milligrams developed rhabdomyolysis, which resolved after pravastatin and gilteritinib discontinuation. Our clinical study protocols incorporate routine laboratory assessments, including CK.

Finally, an exposure-related association between gilteritinib and AST elevation was also observed. The incidence of grade 3 and above liver enzyme elevations was low at 6 percent. None were confirmed as Hy's law cases. Our protocols include standard hepatobiliary monitoring.

Now, to briefly summarize our dose selection for phase 3, clinical response plateaus after an initial dose of 80 milligrams. Full-target inhibition occurred in most patients with 120 milligrams. Therefore, 120 milligrams was selected as the recommended phase 3 dose.

Turning now to our ongoing adult phase 3 program, which includes four studies in patients with FLT3-mutated AML, 0301 is in relapse refractory and 0201 is in first-line patients not

eligible for intensive induction. Studies 0302 and 0304 are for maintenance therapy.

To summarize the adult data from study 0101, gilteritinib demonstrated robust anti-leukemic activity in patients with FLT3-mutated AML. Oral treatment was well tolerated. These adult data reassure us it is reasonable to consider studying gilteritinib in children.

I will now discuss our proposed pediatric plan. The goal of our pediatric development program is to provide sufficient data to inform a label in this orphan disease population. We are considering two studies with gilteritinib in combination with chemotherapy. We are also conducting a non-clinical juvenile toxicology study, and we are developing a pediatric formulation.

We propose using historical control for both studies. We are proposing this based on expert feedback in light of the poor outcomes typically seen with standard therapy, the promising adult data seen with FLT3 inhibitors, and the relatively

small number of patients, approximately 100 new cases each year in the United States.

Study 0603 would be an open-label, single-arm phase 1/2 study in patients diagnosed with FLT3-ITD mutated AML who have relapsed or refractory to induction therapy. We anticipate enrolling up to 21 patients in phase 1 and 40 patients in phase 2; age, 6 months to 21 years. Enrollment of children less than 2 years of age is contingent upon acceptable juvenile toxicology.

Gilteritinib would be added to the FLAG-DNX backbone chemotherapy of fludarabine, cytarabine, GCSF, and liposomal daunorubicin. Disease evaluation will be performed after cycle 1 to determine disease progression and recommended dose.

After cycle 2, response evaluation will be performed to assess anti-leukemic activity. Phase 1 will establish the recommended phase 2 dose for gilteritinib through a standard 3-plus-3 patient cohort dose escalation design.

The starting dose in children will be 40 milligrams per meters squared. This is

approximately equivalent to 80 milligrams daily dose in adults, which is one dose level lower than the starting dose in the adult phase 3 studies. Investigators will be allowed to de-escalate and escalate based on toxicity. The final recommended phase 2 dose will be based on an acceptable safety profile and biologic activity, as measured by plasma inhibitory activity assay.

Phase 2 will evaluate CRc rate in a two-stage open-label study of 40 patients. The primary endpoint will compare the CRc rate after two courses of gilteritinib plus chemotherapy against a historical response rate of 35 percent in this population.

With a type 1 error rate of 5 percent, we anticipate 80 percent power to detect a 21 percent increase in response rate.

Now, let's turn to our second proposed pediatric study. Study 0604 would be an open-label parallel-group phase 2 study in patients newly diagnosed with FLT3-ITD mutated AML. We anticipate enrolling approximately 56 patients per arm, age

6 months to 21 years. The starting dose will be the recommended phase 2 dose from study 0603.

The current proposal is to enroll from within a larger pediatric oncology cooperative group study. On day 11, children with FLT3-ITD mutated AML will have gilteritinib added to their backbone therapy, depicted here as arms C and D.

This plan allows the children to get immediate treatment while awaiting test results. Note that this design is similar to recent pediatric cooperative group trials in this population.

In study 0604, gilteritinib will be added to induction and intensification therapies as well as maintenance after chemotherapy or stem cell transplant. Since even with transplant there is a very high risk of relapse, a safety run-in will confirm the tolerability of gilteritinib with each chemotherapy regimen.

The goal of study 0604 is to determine the efficacy of gilteritinib in combination with standard treatment relative to historic control.

The primary endpoint in study 0604 is two-year event-free survival. Key secondary endpoints include complete remission and overall survival.

Here is the proposed timeline for pediatric development. We expect the results of our first adult phase 3 study, 0301, in mid-2018. Pediatric study 0603 would start in late 2018. A pediatric unflavored mini-tablet is expected to be available.

Non-clinical juvenile toxicology available by the end of 2018 would hopefully support the inclusion of children 6 months to 2 years. A flavored mini-tablet, which may be suspended in water, is planned for the first half of 2019. Pediatric study 0604 would start in late 2020 after the recommended phase 2 dose is determined in study 0603.

Now, to conclude our presentation, in adult patients with FLT3-ITD mutated AML, gilteritinib has encouraging single-agent anti-leukemic activity with an acceptable and well-characterized safety profile.

It is anticipated that our pediatric plan

would generate sufficient data to inform prescribers in this orphan patient population. We will assess safety, anti-leukemic activity, and pharmacokinetics in our proposed studies.

Given the known cardiotoxicity of daunorubicin, we specifically plan to monitor for cardiovascular toxicity when combining with gilteritinib. Assessments for efficacy will include remission rates, event-free survival, overall survival, and molecular response.

We look forward to your input, discussion, and questions. Thank you.

Clarifying Questions from Subcommittee

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

DR. ROTH: Bruce Roth, Wash U in St. Louis. I had a question just in general about feasibility here. I mean, you say in your own data, there's

730 new AMLs in the pediatric population a year and somewhere between 6 and 22 percent had FLT3 mutations. Let's use 10 percent because math is not my strong suit. That's 73 patients a year.

Then you talk about the subset of those that has relapsed or refractory disease, at least for 0603, and so you're talking about 0603 maybe using 60 patients, 0604 using over 100 patients with those two trials, overlapping by a couple years.

It almost seems overly daunting that you need to have the vast majority of patients in this country going on one of these two trials to pull it off in that period of time.

DR. KRIVOSHIK: Thank you for that comment, and actually that highlights two main aspects in terms of our overall pediatric program. As you've highlighted, it's a challenge from a feasibility perspective to come up with an appropriate timeline to deliver hopefully meaningful results that can be impactful for patients.

That's specifically why, even though the current protocol designs are still very much in the

early state, for both the 0603 and the 0604, we're working with -- for 0603, we're working with TACL and BFM in Europe, and with 0604, we're working with the Children's Oncology Group.

So from a feasibility perspective, I acknowledge the concern you have because it's actually a concern we have, which is, will we be able to deliver data in a very timely manner that can be impactful for patients.

But specifically, that's why we're engaging with the cooperative groups early to figure out what would be an appropriate study design in both relapse/refractory setting and the frontline to bring data hopefully that can be impactful.

DR. GORE: A couple of questions. You have, just going back to your kinome inhibition, you have low nanomolar potency against AXL as well.

DR. KRIVOSHIK: Yes.

DR. GORE: So what kind of work have you done to show that this is an independent FLT3 factor, knowing that AXL has pure inhibition against AML as well? Or what will you plan to do

to look at that in your trials?

DR. KRIVOSHIK: If I can briefly comment on our understanding of the role of AXL within gilteritinib and then specifically come back from a planned, I think, biomarker strategy maybe in terms of what you're getting at in terms of emergence of resistance factors, et cetera.

So AXL in and of itself tends to be associated with drug resistance as a potential mechanism after chemotherapy. Our understanding from our non-clinical data is that the primary mechanism for the anti-leukemic effect is from its FLT3 inhibition.

In terms of looking at restoration, if you will, after, say, using an AXL inhibitor post-midostaurin resistant cells, you're right in the sense that we do have some non-clinical data that shows that, in that particular setting, gilteritinib still has some activity.

But specifically from a mechanistic perspective in the clinic, I think it's very difficult to tease out the relative contribution of

FLT3 relative to AXL in that setting, other than to note that on all of our non-clinical as well as early clinical data, it appears that FLT3 inhibition is an absolute requirement and primary driver in there.

DR. GORE: Can I ask just an additional question? The respiratory failure that you noted in your adult trials, is there a common theory about that mechanism of action? What do we know about those respiratory failures?

DR. KRIVOSHIK: Right. To comment further on respiratory failure, I invite Dr. Ahsan Arozullah up to the podium.

DR. AROZULLAH: As we described, this data is from our 101 study, which is in refractory relapse patients. In that population, we did not see a consistent pattern amongst these respiratory failure patients that would tie together our mechanism. Most of these cases were patients who are either in sepsis concurrently, many infectious sources, pneumonias, and so on. But we did not see necessarily cases of things like interstitial lung

disease in the background behind that.

DR. DuBOIS: Steve DuBois, Dana-Farber, Boston Children's. I have a few questions. First, rather impressive with a patient on it at least out to three years and I'm wondering what you're learning about mechanisms of secondary resistance to the agent.

DR. KRIVOSHIK: So we're fortunate to have a number of patients now that have been on for quite long periods of time. The biomarker strategy in terms of understanding potential resistance mechanisms, there's no clear data at this time from the adult studies, but that is something that we're continuing to assess and then actually have built in with the pediatric trials as well as the adult trials, specifically from a biomarker strategy to try and understand that, but right now don't have a definitive answer in terms of why those subsets do so well for so long.

DR. DuBOIS: And then a follow-up question, the starting dose that you've proposed -- and if I take your 120-milligram flat dose and normalize it

to a body surface area average for an adult, I get 70 mgs per meter squared. So a starting dose of about 40 mgs per meter squared is about 57 percent of the adult dose, which feels a little bit low for a starting dose. I wonder how you came to 40 mgs per meter squared for your starting dose.

DR. KRIVOSHIK: Right. The first thing to keep in mind is the 0101 data is in a monotherapy setting, so that also potentially factors in. The second is that with respect to 0603 and 0604, those will be in combination.

The 40 milligrams per meter squared is roughly equivalent to the 80-milligram daily dose in adults. And that was using a BSA conversion of 1.73. That was the one that we used as a standard. And the pediatric starting dose level lower than 60 mgs per meter squared is roughly equivalent to the 120-milligram dose, if that makes sense. About a 20 mgs per meter squared delta will take you from the 80 mgs, which is that one dose level below our recommended phase 3 dose. Is that clear?

DR. DuBOIS: Thank you.

DR. RAETZ: Elizabeth Raetz, University of Utah. I had a similar question about the rationale for the starting dose. And I just had a question, too. So it sounds like in your adult trial, the 120-milligram dose, anything at that level or higher, you had full target inhibition.

DR. KRIVOSHIK: Yes.

DR. RAETZ: Did you have a good target inhibition at the 80-milligram dose as well that would be the starting-dose equivalent for the pediatric population?

DR. KRIVOSHIK: So to provide -- the short answer is, yes, we had some target inhibition, reasonable target inhibition, but because of some PK variability, unlike the 120-milligram dose where we had near 100 percent inhibition, the 80-milligram dose by plasma inhibitory assay was less than 100 percent, but still very robust.

DR. WEIGEL: Hi. Brenda Weigel, University of Minnesota. I may have missed it, but in your relapsed refractory trials, did you exclude patients who had prior TKI therapy with FLT3

inhibition? And can you speak to -- did all of the patients have prior therapies with other TKI inhibitors or is there a mixed population? Can you speak to that? And with regards to the pediatric trial, is prior exposure, regardless of agent, allowed or not allowed?

DR. KRIVOSHIK: That's a very critical point. In terms of prior TKI on the relapsed refractory population, it was actually allowed. The vast majority of the patients who had a prior TKI were exposed to sorafenib.

When we looked at the overall response rate in patients with prior TKI use, it was 42 percent, which was comparable to the TKI-naïve population of 56 percent. And I believe, just last night, released in Lancet, that data, which was in press, so there's a lot more detail around that, that was released yesterday.

DR. PAPPO: Alberto Pappo. Did you see responses both in patients that have ITDs as well as TKDs or just patients that had internal entire duplications?

DR. KRIVOSHIK: So the majority of the responses that we saw were in the ITD population. We did have very few patients who also responded with the TKD, but that response rate as a fraction of patients was much lower.

It seemed to be driven more by those that had had very high FLT3-TKD ratio, were the ones in that group. And again, that's also something that is in that same manuscript that came out last night.

MS. PREUSSE: Quick question. Courtney Preusse, Fred Hutch. Study 101 does, a tremendous job of describing the use of this drug in a monotherapy context. I guess I'm confused by what seems like a leap to study 604 by combining it with other treatments, other treatments that are known to have high toxicity.

So I guess it's really a multi-part question. How did you make that bridge from monotherapy to combination therapy, and do you have any data on adverse events with regard to combination therapy? And, I'm sorry, can you speak

to also the 7 deaths in the study? I don't remember the slide.

DR. KRIVOSHIK: So let me parse that into -- I grabbed three separate concepts, and the first is what combination data that we have available. And we actually have, although it's still very much in preliminary stage, a study called 0103, which should report out, hopefully later this year and in time for ASH, where we're combining with cytarabine for 7 days plus idarubicin and adding gilteritinib on top of that.

The initial schema had gilteritinib starting on day 1. It was very difficult to tease out from the toxicities from the cytarabine and idarubicin, what was going on with gilteritinib in that setting.

Although we saw in that first cohort 2 DLTs of left-ventricular ejection fraction decrease and hematologic recovery delay, we amended the protocol to do a combination sequential method so that we could actually put windows around when the different drugs were given to try and tease out a

little bit better in terms of understanding the dose-limiting toxicities.

Since amending that protocol, though the data is very preliminary and under review, we've cleared the 40-, 80-, and 120-milligram cohorts, and that data is still accruing. So that will be one element that will help inform when we continue to work with both BFM, TACL, and COG for the combination strategy.

The second component in terms of why not, I think you were implying, but why not just do a monotherapy setting in that population? And I think, right now, back to a study design and feasibility question, this is where we have been guided from our external collaborators.

So obviously, we are happy to entertain different study designs in terms of how to get the meaningful data that we need to actually demonstrate activity in this patient population. But right now, I think the group as a whole that we're working with are leaning more towards going into combination.

That's, I think, partly the feasibility question as well as with the encouraging adult data, and adding to a backbone sometimes is a little bit easier than doing a de novo.

Then your third question around the depths in a little bit more detail, again, I'd like to invite my pharmacovigilance colleague, Dr. Ahsan Arozullah, who will provide as much detail as you'd like to know about those.

DR. AROZULLAH: Ahsan Arozullah, medical safety from Astellas. We have had this concern throughout the 101 study, knowing that there may have been an effect with the QT prolongation

So in terms of following these patients, the particular patient that was reported as a sudden death was a patient who passed away at home. All of that patient's study protocol mandated ECGs, did not show QT prolongation. But the last ECG was several days before this patient had passed away at home, and despite our best efforts, we don't have any ECG readings from the time of their actual death.

MS. PREUSSE: But there were 7 deaths, not just 1. Right?

DR. AROZULLAH: Yes. Apologies. I thought you were referring specifically to the case that was reported as sudden death.

So there were 7 deaths that were assessed. Your attention to the slide that this is a summary of those 7 adverse events that led to death. There was a case of intracranial hemorrhage again in a patient with refractory/relapsed AML. That patient also had a low platelet count concurrently with that.

There was a case of septic shock. There was a case of hemoptysis, and this patient as well had -- with this underlying AML, the autopsy summary did show some lung involvement of the AML as well and a possible underlying fungal pneumonia.

A patient who was reported and passed away with ventricular fibrillation, this patient was in the hospital, and, again, a potential drug relationship could not be excluded. But this patient also had electrolyte abnormalities that

preceded the reported event and did have some background history related to smoking, cardiac disorders.

The fifth patient with respiratory failure, this case again came in the context of a patient with significant sepsis, and the underlying AML with concurrent plural and pericardial effusions was also considered a potential contributing factor.

The sixth patient who had passed away also had neutropenia at that time, and this patient died with severe neutropenia, anemia, thrombocytopenia. And then the last case was a case that was autopsy found to have a primarily embolism. So those were the 7 cases that we had assessed as possibly drug related in the 101 study.

MS. PREUSSE: So the last follow-up question, and then I'll be quiet, is for study 604, the one in combination with other drugs, other drugs that are known to have very toxic side effects, like with daunorubicin and cyta -- anyway, would you consider a dose escalation in a pediatric

population?

DR. KRIVOSHIK: Right. So let me parse that I think to the underlying question, which is, in 604, although the initial starting dose will be in form from the recommended phase 2 dose from 0603, there is going to be a safety run-in, specifically to look and confirm the safety.

Even though that run-in, if you will, from a DLT assessment or confirmatory period, is really confined currently in the current design to induction 1, the DLT assessment post-induction 1 will also continue.

So in terms of allowing not only for individual patient dose escalation or de-escalation for toxicity, but that data is planned to be continued to be analyzed within that broader context to confirm, if you will, that the dose that was brought forward was correct.

DR. WEIGEL: Brenda Weigel, University of Minnesota. With regards to the CNS toxicity, can you speak to the AML CNS status of the patients enrolled on your current studies? Were they

receiving concurrent intrathecal therapy? And was there hypertension associated with the episodes of PRES?

DR. KRIVOSHIK: Right. So let me parse that and first address the PRES with the 3 patients. So the two that were on the study 101 and the third patient that was from the compassionate access protocol, all of the patients didn't necessarily have the traditional hypertensive run-in up front, although one patient, if I recall, I think was mildly hypertensive at the time of the event, 154 over 82, but not the typical PRES related.

Then the one subject who had a seizure but not confirmed as PRES on day 123, I think at day 120 had intrathecal cytarabine, headache, confusion, or headache-increased blood pressure, but did not meet the criteria at that time for PRES.

In terms of AML status, although specifically CNS recurrence of AML was an exclusionary criteria from the 0101 study, I think the question in terms of when we think about how to

enroll and what patient population for 0603 and 0604, we know from our non-clinical data that although we don't have a formal blood-brain barrier study, we do know from tissue penetration that we do get into the brain and also that from the two clinical episodes of PRES, that that also may be indicative of a drug getting across the blood-brain barrier.

So that may be something that may be helpful in terms of trying to ameliorate potential CNS AML.

DR. GORE: Lia Gore, University of Colorado. To follow the PRES patients, a substantial proportion of your patients had had prior stem cell transplant.

Can you state whether or not the patients with PRES had prior transplant? And if so, what was the distance from their immunosuppressive therapy to receiving the agent? And were they on active immunosuppressive therapy at the time?

DR. KRIVOSHIK: Right. I will again invite Dr. Ahsan Arozullah up to provide a little bit more detail around that, but again, given the timing, we

may have very limited information.

DR. AROZULLAH: Ahsan Arozullah, medical safety. So for those two patients that were in the 101 study with PRES, they were not on other immunosuppressive therapy at the time.

In terms of their transplant history, I am not sure. We don't have that exact information as to the time that they were transplanted at this time. But in terms of the distance from their transplant, it does not appear that either of those patients have been transplanted.

DR. MacDONALD: Tobey MacDonald, Emory University. I know almost nothing about AML, so I had to read a little about this. And I found that there is an FDA-approved drug for AML with FLT3 mutation in adults. How does this drug compare to that one?

DR. KRIVOSHIK: From a mechanism of action perspective, the kinases that are hit with midastaurin appear to be different than the kinases that we hit from the overall perspective, so I think you're referring to midastaurin in

particular.

So I think, although I don't have side-by-side non-clinical comparison, I think the two are potentially very different agents, but really asking in terms of what type of clarification do you want or are looking for in terms of understanding.

DR. MacDONALD: So I'll just follow up. In terms of then feasibility, are there plans for this agent to move forward in those cooperative groups in particular? So is that going to further reduce your numbers?

DR. KRIVOSHIK: I'd like to invite Tim Farber from our regulatory affairs group to comment on the pediatric plans for some of the competitors...

MR. FARBER: Tim Farber, regulatory affairs. So midastaurin has recently been approved in newly-diagnosed FLT3 mutation-positive AML, but the safety and effectiveness of midastaurin in pediatric patients has not yet been established.

Based on public information, we're aware

that they were planning two studies. The first was a study in relapse refractory leukemia. We know that that study was recently terminated, so we're not aware of what those results may mean. They also have another study that's planned in newly-diagnosed leukemia, but there's no information on when that study may start.

DR. ARNDT: Carola Arndt, Mayo Clinic. Can you talk a little bit more about the rationale behind maintenance in your proposal?

DR. KRIVOSHIK: Sure. I think given the high rate of relapse in particular, even post-transplant, even with the adult data, the rationale and particularly because of some of the long-term data we have in the 0101 study, which we allowed them to continue until progression is monotherapy, it seemed both from the adult program, where we have two maintenance trials, but in the pediatric program -- given that high rate of relapse in that particular population, it seemed like a reasonable place to offer maintenance therapy in that setting.

DR. ANGIOLILLO: Hi. Anne Angiolillo from

Children's National. Actually, I just have many questions about PRES, but my prior colleagues, Weigel and Gore, have already asked them, so thank you.

DR. PAPPO: Any additional questions? Greg?

DR. REAMAN: In your adult program, are you using maintenance as well, and is that part of the adult program as well?

DR. KRIVOSHIK: If we could pull back up the adult phase 3 program slide here, both study 0302 and 0304 are in the maintenance setting and specifically addressing maintenance, whereas 0201 is in that low-intensity chemo for patients who can't tolerate full induction.

Then the 0301, which is the one that's most likely to read out and gates the pediatric studies, that's in the salvage setting.

DR. WEIGEL: Can you give a little more detail about where we're at with a pediatric-friendly formulation, suspension and ability to dose very small children?

DR. KRIVOSHIK: Yes. I'd like to invite Dan

Mossman from CMC.

DR. MOSSMAN: Dan Mossman, project manager from our chemistry manufacturing and controls organization. We are developing a 10-milligram mini-tablet that will be used initially for the 0603. We've done palatability studies with that formulation, and we determined that the gilteritinib has a strong taste, so we are not proposing to use that for oral suspension. We're developing a second taste-masked formulation, which will be available in the 2019 time frame that will mask the taste.

DR. WEIGEL: So those will be mini-tabs, like they'll be given by a spoon, et cetera? Is that the concept? Because these are historically really hard to get into suspension. That's why I'm asking.

DR. MOSSMAN: Correct. We're proposing to place them in a syringe, and add a small amount of water, and then suspend it in the syringe, and then administer it in the mouth.

DR. WEIGEL: Great. Thank you.

DR. PAPPO: I have another question regarding maintenance therapy. Do you think that you will have the results of the adult trials, that will be able to inform the pediatric trial? Have you decided to have a maintenance phase or not?

DR. KRIVOSHIK: I think it's difficult with event-driven endpoints to know with great precision. I think the 0302 and 0304 unfortunately probably won't read out until several years after the 0604 study is proposed. But in terms of our overall understanding of, even though not a maintenance trial, from the 0101 data, as those patients continue on, I think that's an important dataset that can inform us, but not from the phase 3 trials.

DR. REAMAN: Just to follow on Dr. Pappo's question, are you looking for toxicity in both the 0101 and the other adult trials with respect to longer-term exposure to this product?

DR. KRIVOSHIK: With the patients we have to date who have been on for quite a period of time, although the numbers are relatively small compared

to the ones who were on early on, just because of the nature of the program, there doesn't appear to be any differences in the emergent new long-term toxicity.

What we've seen in those 9 patients in particular, who have been on for many, many cycles, up to 3 years, is that the adverse events that come in reported look almost the same as when they first started trial.

DR. ARNDT: Carola Arndt, Mayo Clinic. So in looking at the study design for 0604, if I understand it correctly, once patients are identified to have FLT3-ITD, they will continue on this same backbone of chemotherapy that they were originally randomized to, and then be randomized to either -- and they will all get gilteritinib. Right? Gilteritinib?

DR. KRIVOSHIK: Right.

DR. ARNDT: How would you manage -- the toxicities may be different -- using the agent with "experimental chemo to be determined" versus standard DA chemotherapy? It's almost like a 2-by-

2 design, kind of.

DR. KRIVOSHIK: Right.

DR. ARNDT: How are you going to deal with that in the small numbers?

DR. KRIVOSHIK: Right. And I think that's one of the key pieces that we're working with, the folks from Children's Oncology, particularly Todd Cooper and Jesse Pollard in terms of trying to understand and tease out the design.

The arm D and arm B in particular, the experimental chemo is -- if you look at it in terms of where COG is in terms of the timelines, this sort of falls into the CPX-351 trial, which is very similar in terms of a liposomal cytarabine and daunorubicin.

Whether or not Mylotarg is put in there, I think is the key question. But that's a critical point that you raise, that we're still working with the folks from COG how to figure out what the right combinations are from a safety perspective as well as can you tease out what the magnitude of effect is.

DR. PAPPO: Any additional questions?

(No response.)

Questions to the Subcommittee and Discussion

DR. PAPPO: Thank you very much.

There is no open public hearing session. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers at this meeting that, while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Can we start with the first question, please?

DR. WARD: Please discuss the preliminary pediatric development plan, including the indications proposed for further study and in particular the proposal to study gilteritinib only in children with acute myeloid leukemia that harbors a FLT3-ITD?

DR. ARNDT: I just want to clarify the question. Is that studying it only in children with acute myeloid leukemia and ITD as opposed to

those without ITD or other diseases?

DR. WARD: Specifically with FLT3, other mutations.

DR. ARNDT: As opposed to those that -- AML without FLT3?

DR. WARD: As opposed to potentially studying AML with FLT3-TKD mutations.

DR. PAPPO: How often do you see TKD mutations in pediatrics compared to adults, or is the vast majority of them ITDs? I don't know.

DR. GORE: There are more ITDs, but the TKD mutations are not uncommon.

DR. PAPPO: So potentially, those patients should perhaps be studied with this drug.

DR. GORE: It depends on what data are available, I think.

DR. PAPPO: I'm sorry?

DR. GORE: I think it would depend on what data are available.

DR. PAPPO: Right.

DR. GORE: It's sort of like, was it W.C. Fields, and why did you rob the bank, it's because

where the money is. Actually, I think it's smart to look at a specific mutation that you have data for. It's a little bit hard to know where else this may be applicable, but I think you want your trial to be optimized for success.

So the question is if there are other data that would suggest it could be used in the populations, then that might be worthwhile.

DR. PAPPO: They had mentioned that there were some data with exclusively TKD patients, but I don't know what their responses were. But if there's data available and it looks promising, perhaps those patients should also be included.

I asked that question, and I believe you had mentioned that there was some data with TKD. Correct?

DR. KRIVOSHIK: Yes. But the response rate in that TKD was much lower than -- so for example, in the 0101, those who had FLT3-ITD and TKD, 62 percent -- it was a small subset -- was similar to what was seen with FLT3-ITD only, which was 55 percent.

Those who have the TKD only, the D835 mutation in particular, the response rate was about 17 percent. So it only appears to be, although it's early days in terms of teasing that out, a subset of the TKD patients that seem to respond, but it's a much lower response rate than the ITD.

DR. DuBOIS: I may need some help from my hematologic malignancy colleagues. But I seem to recall some prior data with FLT3 inhibition and MLL-rearranged infant ALL. And I wonder if any of my colleagues want to tell me if that's a good idea or a bad idea, because I just can't remember.

DR. REAMAN: It's not a good idea.

(Laughter.)

DR. REAMAN: At least with the FLT3 inhibitor that was evaluated, I don't think so.

DR. RAETZ: I think, too, probably with that patient population, it would be contingent upon the oral formulation, the pediatric oral formulation as well, but it sounds like that's soon to be available.

DR. PAPPO: Any additional comments?

(No response.)

DR. PAPPO: So if I got this right, everybody's in agreement that it should be used for patients with ITDs. And as additional data perhaps emerges, if there's a subset of patients with TKD, once they flush out the data, perhaps that group could also be targeted.

It's not a good idea to use this drug in MLL-rearranged leukemia. And plans for the pediatric studies should be contingent upon the availability of a pediatric oral formulation, which is currently being worked on. Yes?

DR. REAMAN: I would just caution the second statement that it's not a good idea to use it in MLL-rearranged leukemia, because it really hasn't been evaluated. But I was addressing the issue of FLT3 inhibitors in general in MLL-rearranged infant ALL.

DR. PAPPO: We'll change that. Thank you.

We will now proceed with question number 2.

DR. WARD: Please discuss any potential concerns unique to the pediatric population,

including toxicities that may be seen when gilteritinib is added to multi-agent chemotherapy. Consider whether any pediatric age groups should be excluded from study and mechanisms to minimize risk on the proposed clinical trials.

DR. RAETZ: Elizabeth Raetz. I just had a question. This was probably discussed, but in the design of the relapse trial, was there any consideration to using the agent just with the FLAG backbone alone without the dauno because of potential cardiac toxicity?

DR. KRIVOSHIK: So right now, the current proposal is based on the FLAG-DNX. But I think, again, that's not completely fully locked in, but I think the idea was there to include the daunorubicin as well.

DR. GORE: Lia Gore, Denver. So DaunoXome is uniquely difficult to obtain in the United States at present. So can we assume that that's primarily a European trial, or how are you managing that? And you did mean DaunoXome, not daunorubicin. Correct?

DR. KRIVOSHIK: Correct. And we'd obviously have to work with regulatory authority to work through those details, but the plan right now is to have it as a global trial, not just a European trial with a liposomal formulation.

DR. ANGIOLILLO: Anne Angiolillo from Children's National. I just have to answer this question asking another question, and again, back to the PRES. Would the company expect a higher incidence in the pediatrics compared to adults?

DR. KRIVOSHIK: Our current understanding right now is that we would expect a similar incidence and similar safety profile in pediatrics as we've seen in adults, with that one construct that most of the adult data so far has been monotherapy, whereas what we're proposing in pediatrics is in combination.

DR. GORE: Lia Gore again. Given that you certainly would want a patient to survive long enough to have long-term side effects, do you have potential opportunities to look at some of the more longer side effects that may occur in patients who

might receive this in maintenance, and how are you choosing to look at that in a young and growing developmentally immature organism in terms of thyroid, endocrinologic function, growth parameters, those kinds of things if you're lucky enough to get patients to survive long term?

DR. KRIVOSHIK: I think that's a very important point as we go back and work with our collaboration partners to figure out how best to monitor for long-term effects in the pediatric population.

DR. WEIGEL: To get back to question number 2, I certainly don't think there's any data presented that we should restrict ages. I would encourage standardizing across the protocols, the use of intrathecals. Most pediatric trials will allow intrathecal chemotherapy administration to prevent CNS recurrence.

Given the PRES issue that we've discussed, I think it would be very important to standardize that and to collect that data, as that may or may not be important.

I also think there should be very clear guidelines, given the differences between the relapsed and the upfront trials in the anthracyclines being used, that we need to very carefully assess the cardiac toxicity. And those will be important differences between those two trials.

DR. PAPPO: Any additional questions or comments? So I will try to summarize. I'm sorry. Greg?

DR. REAMAN: Just going back to the first question about the incidence of PRES and then Dr. Weigel's question regarding the IT cytarabine use, do we anticipate that there will be a greater incidence? Because that's not something that was probably a component of the adult studies.

So would there be a need for special monitoring as well as guidelines for management?

DR. WEIGEL: I would suggest at least my impression is that in the adult leukemia world, the use of routine intrathecals is much less frequent, whereas it is standard of care in pediatric

leukemia care. So I think we have to be very careful about that difference.

DR. PAPPO: Any additional comments or questions?

(No response.)

DR. PAPPO: So I'm going to try to summarize this. The first question was whether dauno should be added to the FLAG regimen. It is my understanding that is the current plan. There might be an issue with the availability of this agent in the United States. This appears to be a global study, so the sponsor is currently working on trying to determine how dauno will be made available here in the U.S.

There was significant discussion about side effects of PRES and a question as to whether there was a higher incidence in pediatrics or not. It is expected that it will have a similar safety profile in pediatrics than adults. However, we highly recommend that there are special monitoring rules for this side effect and to also standardize the doses of intrathecal therapy in these patients.

Since patients will be receiving a maintenance phase of this agent, it is highly recommended that you monitor long-term toxicities and you develop a plan for long-term monitoring of these patients with specific targeted toxicities that may be related to this agent.

It is also recommended that there are guidelines for cardiac assessment and monitoring, given the addition of anthracycline and the potential cardiac toxicity of this drug. Anything else? Yes?

DR. REAMAN: Can we just get some clarification? The 0604 is envisioned as a global study, an international study? I thought it was just a COG study.

DR. KRIVOSHIK: 0603, right now we're considering a global footprint. 0604, you're correct, is specifically within COG as being proposed.

DR. REAMAN: So the issue of DaunoXome was here. Okay.

DR. PAPPO: We will now go to the third and

final question.

DR. WARD: Please comment on the sponsor's proposal to include one year of maintenance therapy with gilteritinib monotherapy after intensification to or hematopoietic stem cell transplantation in study 0604.

DR. ARNDT: I think a lot of this has already been discussed, but I guess one comment would be that, again, the toxicity profile might be different for maintenance here in patients who got a stem cell transplant versus the chemotherapy, and that'll have to be obviously sorted out.

DR. GORE: Lia Gore. Is there agreement among your transplant advisors about when maintenance therapy would start and what criteria would need to be met for them to be willing to let their freshly transplanted patients receive an additional medication?

DR. KRIVOSHIK: That's still under discussion right now, but the current plan was shortly after transplant to allow for up to a year in that setting, but there isn't consensus yet, and

the protocol is still very much in the early draft.

DR. REAMAN: I know the numbers are going to be small, but is there any consideration for either addressing the need for maintenance in a randomized or even a stratified manner based on MRD determination at the end of maintenance or after transplantation?

DR. KRIVOSHIK: So we certainly will take that into consideration. I think in terms of particularly that front-line setting, because we're trying to piggyback on top of the COG trial, I think there's a number of unanswered questions, and that's one of the key ones, too. But certainly, if we can figure out a way to make it feasible within that current design, then certainly we will take it under consideration.

DR. PAPPO: Any additional questions or comments?

(No response.)

Adjournment

DR. PAPPO: So if I can summarize this third question, it would be important to look at the

toxicity profile in patients that received transplant versus no transplant, also to better clarify when is this drug going to be started, after BMT. Apparently, currently it's shortly after BMT.

Then the final question is whether you would consider a randomized study, at least in subsets of patients to determine the value of maintenance therapy in this population.

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 very much, and I'll see you all tomorrow.

(Whereupon, at 2:25 p.m., the session was adjourned.)