FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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

Afternoon Session

Tuesday, June 28, 2016

1:20 p.m. to 2:44 p.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

(1:20 p.m.)

DR. PAPPO: Good afternoon. Before we start, I would like to ask Dr. Donoghue to introduce herself.

DR. DONOGHUE: I'm Martha Donoghue with the Division of Oncology Products II.

DR. PAPPO: Thank you. We will now proceed with topic 3, atezolizumab from Roche/Genentech. Dr. Lauren Tesh will read the conflict of interest statement for this session.

Conflict of Interest Statement

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

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

interest laws and regulations.

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

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

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

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for the purposes of 18 U.S.C. Section 208, their employers.

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

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

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

The discussion will also provide information

to the agency pertinent to the formulation of written requests for pediatric studies, if appropriate. The product under consideration for this session is atezolizumab, presentation by Roche/Genentech.

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

Dr. DuBois' waiver involves his employer's current study of atezolizumab funded by Roche, which is anticipated to be between $50,000 and $100,000 per year in funding.

Dr. Neville's waiver involves her employer's current study of atezolizumab funded by Roche, which is expected to be between zero and $50,000 per year in funding.

Dr. Dunkel's waiver involves his consulting

agreement with a potentially affected firm in which he receives between zero and $5,000 per year.

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

Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857 or a request may be sent via fax to 301-827-9267.

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

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

Dr. Morrow's role at this meeting is to

represent industry in general and not any particular company. Dr. Morrow is employed by Amgen.

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

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

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

For this reason, FDA encourages all participants, including the sponsor's nonemployee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed to the sponsor's presentation.

Industry Presentation - Raphael Rousseau

DR. ROUSSEAU: Thank you very much. Ladies and gentlemen, this is my great pleasure, on behalf of my team, pediatric development oncology team at

Roche/Genentech, to discuss with you today atezolizumab oncology development in pediatrics.

This is particularly important for us as we're trying to develop a comprehensive pediatric drug development program that goes beyond atezolizumab. It is important for us today to be able to share that with you.

I will start my presentation by introducing my team. I'll cover cancer immunotherapy and the differences between adult and pediatrics. I will review some aspects of our atezolizumab program in adults, its mechanism of action, and its adult development.

I'll show you some key differences that we perceive in the development of atezolizumab in children and adults. Then I'll spend some time detailing our ongoing phase 1 trial in children with multiple different tumors.

Then I'll share with you some aspect of the next steps that we would like to move on further on after we develop that drug in the phase 1 space.

This is our team at Genentech and Roche.

I'm pretty proud of having gathered a number of pediatric experts. I think this is unique in industry to have such a drug development team thoroughly dedicated to the development of new compounds for children with cancer.

We really look at a vision that goes beyond the regulatory obligation, looks at the mechanism of action of our compounds, and tries to address the unmet medical needs across the different tumor types affecting children, especially rare ones.

We have several goals, and I'd like to point out the one that I think is closest to my heart, as a pediatric oncologist. It's been frustrating in academia not having access early on to those drugs -- is to provide early access as early as we can. As a matter of fact, the program that we'll develop today has been started in children before we get approval in adults.

Many of you are aware of the recent success of cancer immunotherapy. A number of landmark publications have now reported very compelling results in the adult space.

The concept is really to activate the patient's own immune system to reject its own tumor cells. A number of steps are necessary for this to occur. It starts at the level of cancer cells that need to release cancer cell antigens, if they exist.

Those antigens are then presented to the immune system. There's a step of priming and activation of the immune cells so that they can then traffic and go back to the tumor, hopefully recognize cancer cells, and destroy them.

As you're aware, novel treatment modalities have been developed in the immunotherapy space. One of them is immune checkpoint inhibitors, and atezolizumab, that I'll often refer as atezo, is acting at the end of this activation cycle, helping T-cells to recognize cancer cells and hopefully destroying them.

How does that work? Atezolizumab is a humanized monoclonal antibody that inhibits the binding between PD-L1 and its receptors, PD-1 B7.1.

PD-L1 is expressed on a number of tumor

cells, but also on some immune cells. It prevents activation of the immune system in recognizing tumor cells and destroying them.

The hypothesis that's now been confirmed in many adult tumor types is that by blocking PD-L1, we can restore this T-cell recognition of tumor cells and generate priming of those T-cells so that they ultimately recognize and kill those tumor cells.

Of note, atezolizumab also leaves the PD-L2/PD-1 interaction alone, which can have some interesting features on maintaining immune homeostasis.

The compound has now been tested in more than 5,000 patients, adult patients across a number of clinical trials as of February 2016. The safety profile is quite acceptable across tumor types.

Most of the adverse events are grade 1-2. They are immune-related events, and you can see a number of them listed here. They are manageable by withdrawing atezolizumab or using supportive care.

The safety profile appears similar across

tumor types, suggesting that there's independence from the level of PD-L1 expression. There's no apparent dose-related trend on the incidence of these adverse events.

Now, we have a pretty robust clinical program in place in adults. More than 50 clinical trials are ongoing. We've seen a number of positive signals.

We have three pivotal trials ongoing, one in melanoma, another one in renal cell carcinoma, and one in triple-negative breast cancer.

The FDA has granted atezolizumab with a breakthrough therapy designation for a metastatic urothelial cancer, which led to approval of atezolizumab under the name of T-Centrique as of May of this year.

We've submitted the biologic license application last February for the treatment of adult patients with non-small cell lung cancer, and there, as well, the FDA granted a breakthrough therapy designation.

Looking at some of the data for this

non-small cell lung cancer application, here is the Kaplan-Meier curve of the POPLAR phase 2 randomized trial in previously treated adult patients with non-small cell lung cancer.

You can see from the hazard ratio that the patients treated with atezolizumab do derive significant clinical benefit, hazard ratio of 0.69, which translates into a three-month benefit, which is clinically significant, as well as statistically significant.

Looking deeper into the data from that POPLAR study, I'd like to point out some interesting features regarding PD-L1 expression level.

On the right-hand side of this slide, you see the threshold of PD-L1 level that we're using to determine the expression of tumor cells, but also on immune cells infiltrating the tumor.

What you can see on the left-hand side is that across the different subgroups of PD-L1 expression on tumor cells or immune infiltrating cells, you see hazard ratios that are clearly

showing that there is a positive effect of atezolizumab on those patients.

I think quite importantly to note is the fact that even in patients who do not express PD-L1 on their tumor cells or either immune cells, the TC-0 and IC-0 that you see at the bottom of the plot, there's still a clinical benefit that is at least equivalent to docetaxel, which is an approved chemotherapy in that setting with a known safety profile.

I think this is very encouraging to us to have this all-comer approach because if we didn't have such an all-comer approach, we would've missed this clinical benefit. I think in light of what we want to do in children, I think it is important to note this effect also occurring on PD-L1-negative patients.

Moving on, in designing our clinical program in pediatrics, I'd like to point out a number of differences between adult and pediatric cancers, which we think are important to consider in the design of the study.

First, you probably heard about mutational load as being an important characteristic or predictive marker for clinical responses in a number of adult tumor types, including melanoma and non-small cell lung cancer.

Here, you can see on this graph, the frequency of mutation in different tumor types. On the right-hand side of the graph, you see mainly adult tumors. Boxed in red are more pediatric tumor types.

You can see that the frequency appears to be lower in children. There is a hypothesis that maybe with a lower mutational load, there may be less expression of neoantigens, in turn, capable of generating the primary immune response.

We feel that this is a hypothesis that we have to explore in a proper clinical setting, because we know that from certain adult tumor types, such as renal cell carcinoma, which doesn't have a very high mutational load, we still see some very important immune responses.

Secondly, it may not be only around the

quantity of neoantigens, but also the quality of neoantigens. Despite the fact that pediatric tumors may harbor less mutation than their adult counterparts, it is an important hypothesis that needs to be tested in a phase 1 setting and collecting information, biological and clinical information, to confirm or inform that fact.

The second thing that I wanted to point out, and this has been shown in a number preclinical series in pediatrics by us or others, PD-L1 expression on tumor cells is very different between adult and pediatric tumors.

The left image shows you the brown staining PD-L1 marking on tumor cells of a colon cancer biopsy in an adult patient, which is notoriously different than the pediatric rhabdomyosarcoma slide that you see on the right.

This is a known fact. PD-L1 expression is apparently lower in children. As we've seen from the clinical outcome of our non-small cell lung cancer trial, some patients with negative PD-L1 expression do present with a clinical benefit.

We don't think this should be a hindrance to proceed with a well-designed phase 1 trial looking at clinical outcome, as well as biomarker outcome for this pediatric population.

Finally, I'd like to point out one very important feature is the presence of resident T-cells at baseline in those tumors. As you can see here on the left-hand side, this is the CD8 marking, the brown staining shows T-cell infiltration both in colon cancer, this adult tumor type, and rhabdomyosarcoma.

The level of infiltration may be slightly lower in pediatric tumors, but we do see this tumor infiltrate in the biopsies that we've obtained from a large series preclinically and prior to our clinical trial.

We feel that this is encouraging. T-cells are there. The PD-L1 expression may not be as high or may be absent, but we do see some benefit in adult patients even if they have PD-L1 negative tumors.

With this mind, we decided to conduct a

broad spectrum biomarker trial looking not only at PD-L1 expression and CD8 T-cell infiltrate, but also a number of biomarkers that we can further discuss after my presentation in an otherwise unselected pediatric population so that we really ensure that we don't prematurely exclude any children who could potentially benefit.

We're talking here children with high unmet medical need, not only because they have rare tumors, but because they are relapsed or refractory with no other treatment option.

The idea is really through this clinical trial to collect robust data, including biomarker, to really optimize our biomarker assessment and further refine the inclusion criteria when we move forward in phase 2 and beyond.

Those biomarker findings are critical, and there's not enough preclinical data that we can really use now to really determine what is the best biomarker. That was a question raised by the FDA, and we can further discuss that after my presentation.

We feel that this all-comer approach, with a robust biomarker program, is really the best way forward.

This is the ongoing phase 1/phase 2 clinical trial that we've started as part of our iMATRIX platform that we'll describe later on. This is a single-arm study designed to evaluate the safety, tolerability, pharmacokinetics, immunogenicity, and preliminary efficacy across a number of tumor types in children, adolescents, and young adults.

I think you'll agree with me that young adults usually don't have much therapeutic options, and so we've decided to raise the age of accrual up to 30 years so that adults with relapsed-refractory pediatric type tumors can participate in the trial. Those patients have no other therapeutic options.

As I mentioned, PD-L1 expression is not required, but there is a mandatory biopsy at study entry or access to archival tissue so that we can assess the biomarker signature.

Atezolizumab is administered intravenously every three weeks while experiencing clinical

benefit. The dose for children below the age of 18 years is 15 milligrams per kilogram, and this is based on model and simulation of the totality of our phase 1 adult program looking to match exposure observed in adults.

Above 18 years of age, the dose is the dose that is now approved in adults of 1200 milligrams. The primary endpoint beyond PK and safety are overall response rate and progression-free survival. The secondary efficacy endpoints are the duration of response and overall survival.

This is a gated study design, again, as part of our iMATRIX phase 1/phase 2 platform. Really, the intent is to limit the number of patients exposed across the different tumor types so that we really expand into cohort expansion if we see a number of pre-established responses.

This is based on historical controls that have been discussed with our colleagues from the academic consortium participating to the study so ITCC in Europe and POETIC in the United States.

There's a first phase of PK and safety

assessment in a minimum of 20 patients for early PK and safety evaluation. Then we evaluate response for approximately 10 patients per tumor type. Then the decision to continue to enroll is really based on whether or not enough patients, two to three, generally, depending on the tumor types, have presented with an objective response.

There's the retrospective biomarker analysis, which ultimately should help us to decide whether or not to enrich certain cohorts based on the biomarker signature.

This is the status of the trial. We started enrolling in November of last year. We, as of June, had 67 patients enrolled in more than 8 tumor types. As of yesterday, we have 73 patients enrolled, median age of 14 years, age ranging from 2 to 29 years.

An indefinite data monitoring committee has allowed us to now enroll children below the age of 2, but we haven't yet enrolled such patients. They are very rare in the relapsed setting.

You'll see on the right bottom hand side of

the slide that a number of tumor types, including very rare ones, have been enrolled on that study, which I think is quite remarkable considering the rarity of those tumors.

The iDMC has also looked at the first 20 patients in terms of safety and PK and has given the green light to continue at the same dose without any modification to the trial design.

Where do we want to go next? We realize that atezo is just one potential step to activate the immune system. There are a number of other therapeutic modalities that could be very helpful in combination with atezo to activate the immune system and propagate that immune response.

A number of them are listed here, ranging from conventional chemotherapy, radiation therapy, or some of the compounds in our own portfolio.

We heard this morning about two very interesting compounds that could be also combined with atezo. There are a number of options. We're not yet at a point where we can decide which combination is going to be the most effective in

children. As you know, immunotherapy is very difficult to modelize in preclinical models.

We'll use the totality of the data. We'll follow the science using data coming from the adult combination trials and any evidence that we can find in the literature to combine those therapeutic modalities in a very selective manner in children with high unmet medical need.

I'd like to point out, though, that we don't have the luxury, as our adult colleagues, to test so many options in those rare patient population. So we'll really need a mechanism by which we can prioritize the best options for those children.

With this in mind, I'd like to spend a little bit of time on our iMATRIX trial concept, which we think can help prioritize in a rapid manner the best single agent and hopefully the best combination.

To many of you, this is nothing new. This is what we've been doing in academia for many years. What we bring with that concept, I think, is a layer of regulatory science that we hope can

help accelerate the implementation of this platform across many study sites, and we currently have more 40 sites in Europe and the United States, and bring drug in and out very quickly using a master trial concept that is now being discussed with the European Medicines Agency and the FDA.

We hope that with this rigorous concept, looking at pre-established response rate, discuss with academic experts and regulatory authorities, we'll be able to move forward very quickly in the pediatric space, focusing really on pediatric tumors as opposed to looking at an adult tumor and its potential equivalent in children. We hope that this approach -- and we've now shown it with atezolizumab with 73 patients in less than 6 months.

We've started another arm using our cobimetinib, a MEK inhibitor compound. We've recruited now one patient in the United States. Some of the other compounds that I've shown you on the previous slide, once have passed phase 1 and early phase 2 in adults, could come on that

platform as well.

This is also a concept that we would like to share with other sponsors, that we all use the same gates in all the same response rates, so that we can have the same conversation on how to prioritize those different compounds moving forward.

The key takeaway for today's presentation, atezolizumab is a humanized monoclonal antibody that has shown some quite interesting responses, both from a clinical efficacy standpoint and safety standpoint in many adult tumors.

It is now registered for administration in patients with metastatic urothelial cancer. It is well tolerated, and we've started a voluntary pediatric program that is now approved as a PIP in Europe as part of our iMATRIX platform, with the intent of really matching those promising molecules to pediatric patients with rare and high unmet medical needs.

We have a rigorous and consistent PK evaluation. Efficacy gates have been defined and approved by health authorities. We have a

comprehensive biomarker evaluation program, a strong collaboration with our academy colleagues.

We hope to come back to you in the near future, probably by the end of the year, with efficacy and safety results on that program in order to decide what are the next steps that we should envision, either as single-agent or in combination.

With this, I hope that I have reassured you that despite all the frustration that we have as pediatric oncologists of not getting those drugs early enough, we are, I think, going the extra mile to make this available to the community through this iMATRIX program.

With my colleagues, experts in pediatrics or in the atezo adult program, we look forward to your questions. Thank you very much.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you very much. There are no OPH speakers, and therefore, we will now take clarifying questions for the sponsor.

Please remember to state your name for the

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

DR. DuBOIS: Steve DuBois, Dana-Farber. Thank you for that presentation.

I wondered if you might share what's known about the benefit of PD-L1 inhibition versus PD-1 inhibition. You touched on it briefly in your presentation, but I'm wondering if there are -- really what's done about that preclinically or even clinically.

DR. ROUSSEAU: As I mentioned to you, initially, our assumption that by sparing the PD-L2 pathway, we may maintain -- sorry.

Can you project that slide, please?

We may spare the PD-L2 pathway and thus maintain a homeostasis and reduce autoimmunity. For what we know from the current adult trials testing both PD-1 and PD-L1, we haven't seen yet that difference in the clinical setting.

DR. PAPPO: Thank you. Ira?

DR. DUNKEL: Ira Dunkel, Memorial Sloan Kettering. Raphael, I had a question about the

design of the pediatric trial. If I understand correctly, there was a phase 1 and phase 2 component. To me, it seems admirable that you elected to include young adults up to 30 with pediatric tumors in the phase 2 component.

But it seems like -- there's obvious rationale for why you'd include young adults in the phase 1 component when you already had phase 1 data from adult trials.

Why didn't the phase 1 study restrict itself to under 18 or maybe even pre-adolescence?

DR. ROUSSEAU: Yes. We really wanted to give an opportunity for young adults to participate to the trial early on. Now, we had provision in the clinical trial, in the protocol, that if too many adults were participating in the phase 1, we would limit the study entry to favor younger patients.

That didn't need to occur. We were able to accrue data from younger patients. But you're right, this could have been an issue, but we had planned for that.

DR. PAPPO: Thank you. Dr. Weigel?

DR. WEIGEL: Raphael, thank you very much. I have a few questions. We're targeting with PD-L1 the tumor side rather than the PD-1, the immune side. There is a little bit of data known about PD-L1 expression on pediatric tumors, but not a lot.

There's a lot of heterogeneity. You have some data to suggest that response may be slightly correlated with expression of PD-L1. Can you speak to, with the antibody and a dose, the saturable relationship between the amount of expression of PD-L1 on the tumor cells and the amount of saturability and dose-targeting in dose-finding that was done to optimize response?

DR. ROUSSEAU: Yes. I'll ask Dr. Cathrine Leonowens, our clinical pharmacologist, to answer your question.

DR. LEONOWENS: Hello. My name is Cathrine Leonowens. I'm the clinical pharmacologist on the pediatric atezolizumab study.

As we heard from Dr. Rousseau, the pediatric

expression of PD-L1 is different than in the adult population. Further, we weren't really sure how atezo would behave with respect to pediatric tumors.

The only way that we could bridge the dose was based on exposure, by matching the exposure in pediatric patients to exposure that we had observed in adult patients and exposure at which we had seen responses in adults.

What we did, when we were developing atezolizumab in adult oncology patients, we developed a pharmacokinetic model, and we used that model and allometric scaling based on body weight to test out a few different doses. We arrived at a 15-milligram per kilogram dose, which was a good balance between safety and a reasonable expectation that we would match adult exposures.

We've been gaining PK data, and we have some that does confirm that the 15-milligram per kilogram dose is reaching exposures in pediatric patients that match those that we've seen in adults.

The other important thing to note is that these concentrations that we're observing are also well above saturation, and so we know that we're achieving adequate exposure in the pediatric population.

DR. WEIGEL: Thank you. A follow-up on that, as we know from other studies using antibodies in children that small children tend to potentially have a higher clearance of the antibody and may require higher dosing.

Are you looking at that at all in your assessment and doing any sub-analyses to ensure that the younger, smaller patients are actually meeting the same exposures?

DR. LEONOWENS: Yes, we are. The initial dose is 15 milligrams per kilogram, but there are provisions in the protocol by which we're analyzing the data in as real time as possible. We are assessing the PK data as the patients complete their cycle 1.

There are provisions in the protocol that allow for a dose modifying if we see that the

younger, lower-weight patients aren't matching that exposure.

That said, once the study has completed and once we continue to enroll patients in the second phase of the study, we do expect to collect sufficient data in younger patients to adequately characterize the PK.

We will be doing sub-analyses based on body weight, among other disease covariates and population covariates to really understand how the drug is behaving in pediatric patients.

DR. PAPPO: Thank you. Dr. Adamson?

DR. ADAMSON: A couple of protocol, logistic, technical questions, and then a comment on timing.

When is this trial negative? I think you listed about eight histologies there, and your histologies are diagnostic. But histology is a two-stage. You have to pass stage 1.

Is there a point in time where none of them pass, or how many of them have to stop before you say this is not an effective active agent in this

way in this disease?

DR. ROUSSEAU: The protocol states that we need to have at least two cohorts of 10 patients so that we have given enough chances even to rare tumors to reach the gate 2 where we can assess response.

We are almost there and across many different tumor types. Some have enrolled already the 10 patients, others haven't. It's too early to say, because as you probably know, immunotherapy takes time to deliver some potential responses.

We looked at six-month responses, and so we haven't reached that point yet. We should reach it by Q3 of this year. It's too early to say across some of the tumor types that have enrolled quicker than others.

DR. ADAMSON: Is there an a priori? If we fail in X histologies, we're done?

DR. ROUSSEAU: No. The concept here is not only to look at the response with single-agent and those heavily pre-treated patients; we look at the totality of the data. We look at the biomarker,

and we'll come back and discuss with you where it makes sense to eventually continue in combination, not a single-agent, but in combination, even if we don't see any responses in some tumor types.

Again, this is not yet the point where we can discuss those results.

DR. ADAMSON: The logistics of this, was this part of the master protocol for iMATRIX? If so, how is that handled? Is that a stand-alone sub-protocol or was this one a stand-alone protocol following the design?

DR. ROUSSEAU: This is a stand-alone protocol as it is now. We had discussed with a number of advisors as to whether or not we should first have the master trial discussion with health authorities, and then put the atezo program and the cobimetinib program on the master, or whether we should start that separately.

We've decided to the latter, start atezo, start cobi and then use them as examples for the discussion on the master trial. The master trial discussions are currently being discussed with EMA

and FDA, but we started as stand-alone for atezo and cobimetinib.

DR. ADAMSON: The last one is a comment. The Roche/Genentech team, I think, certainly, based on my knowledge, is one of the more advanced pediatric dedicated teams across the industry and is certainly to be commended for that work.

With that said, I think this drug -- and it's not alone. There's a long list. It highlights some of the limitations that we're having with the regulatory requirements and incentives as far as getting therapies, high priority treatments early into clinical trial, be it at the EMA, with PIPs, or the BPCA. As Greg said, PREA doesn't apply.

The number that struck me was over 5000 adults and 70 children. That's not early access. That's pretty much what we do.

Drugs get approved. Thousands of adults get enrolled. Clearly, an important new modality -- let me be very clear. This is not Roche/Genentech. This is the landscape.

I don't think we solved the early access problem. I think we now have more dedicated approaches to when we enter pediatric development, how do it, when do it. But 5000 adults, 70 children is not early.

DR. PAPPO: Thank you. Dr. Warren?

DR. WARREN: Kathy Warren from NCI. I presume that PD-1, PD-L1, and PD-L2 in a tumor are not static, but get change over time and with treatments. But yet in your biomarker assessment, which is retrospective, I presume you're going to be using archived tumor tissue, which may be one or two treatments prior to when you're actually treating the patient.

What conclusions can you draw from doing that biomarker analysis?

DR. ROUSSEAU: We do have a provision in the protocol to have sequential biopsy on a voluntary basis. I'll ask Dr. Priti Hegde, our biomarker lead, to give you more details about the biomarker program in pediatrics.

DR. HEGDE: I'm Priti Hegde, and I lead the

global biomarker program for cancer immunotherapy in pediatrics.

What we're trying to do with the pediatric program is really try and learn from our adult program. I'll give you an example of a phase 2 study that we ran in lung cancer where we took archival tumors and fresh pre-dosed biopsies in second-line lung cancer patients. These are patients who have gone through frontline standard of care therapy.

The idea behind doing that was to really understand how variable is PD-L1 expression, as well as CD8 positive T-cell infiltration in patients both in archival tissues, as well as in fresh pre-dosed biopsies.

What we've observed is that, in general, the prevalence is fairly consistent between archival tissue and fresh pre-dosed. Generally, you do see an acute rise in T-cell infiltrates, as well as PD-L1 expression in T-cell infiltrates when you give standard of care chemotherapy.

That lasts for a certain period of time, but

when patients progress, their PD-L1 status tends to come back down to baseline. We've seen about a 75 percent concordance between archival tissue and fresh pre-dosed.

With that experience, we think that we can learn quite a bit just by looking at archival tissues from the pediatric cases as well. Now, having said that, we do have a nonclinical study that we're now looking at, where we are trying to get tissues from multiple sites from patients to understand the variability of PD-L1 expression.

Maybe what I'll do is I'll just give you a quick example on slide 33, if I can get to slide 33.

Here is just one example of three biopsies from a single patient on the pediatric study. What you're seeing on the top panel, biopsy 1, biopsy 2, and biopsy 3 are all three different pretreatment biopsies looking at PD-L1 expression, as well as CD8 expression.

You can see that it's fairly consistent from biopsy to biopsy in this one single case. This is

consistent with what we've seen in adult cases as well.

With this particular patient on treatment, we do see an increase in CD8 positive T-cells in the responding lesions, and those are biopsies 4 and biopsies 5.

The bottom panel there for CD8, the brown dots reflect CD8 positive T-cells, and the enumeration is at the bottom, the blue squares.

The one nonresponding lesion in this tumor here had very little change in CD8 positive T-cell infiltrates. In general, we're now starting to generate more and more data from our pediatric populations to really understand how variable is this expression, both in archival tissues, as well as on treatment with atezolizumab.

DR. WARREN: Can I ask a follow-up? Does it correlate with peripheral lymphocyte counts at all or any peripheral immune markers?

DR. HEGDE: Unfortunately, so far, peripheral biomarkers haven't really been very informative for us in terms of providing

information on response to therapy.

We have identified pharmacodynamic biomarkers in the periphery, but not markers associated with clinical benefit.

DR. PAPPO: Thank you. I had a couple of questions. First of all, I wanted to thank you for not stratifying patients according to PD-L1 expression. A lot of these patients might respond regardless of the PD-L1 expression.

A couple of questions. Why were brain tumor patients excluded? You have a potential population of patients with mish-mash repair that could potentially benefit from this. Was there a specific rationale?

DR. ROUSSEAU: When we started this clinical program, we were concerned about two things. First, usually the exposure to steroids for these patients, and so at that time, we felt that this would be a hindrance to the effect of atezolizumab. This may not be ultimately the case.

Second, we were concerned about safety issues. You probably heard about the concept

pseudoprogression, which especially for infratentorial tumors could generate some pretty bad safety effects when a tumor is growing before it shrinks.

We decided initially to not include brain tumors, but we're in discussion now with study groups to consider inclusion of such patients with supratentorial tumors.

The patient that you just saw actually was a patient with ASPS and brain metastasis. We're starting to accrue some information about safety for intracranial tumors.

I think pontine tumors will remain an exclusion. We're looking into potentially amending the protocol or in a subsequent protocol consider supratentorial tumors.

DR. PAPPO: Another question is, how many types of tumors are you going to evaluate. Is there a pre-specified number of histologies or any solid tumor that initially can -- I guess you've got your first 20 patients already, right? Gate 1? You must be in gate 2 right now with no specific

subsets.

DR. ROUSSEAU: We haven't reached gate 2 yet. We have at least eight different tumor types, and there is no limit.

We had initially restricted to known or expected PD-L1 expression as a requirement from health authorities in Europe, but we also have provision in the protocol to consider other PD-L1 positive tumors, if they happen to be PD-L1-positive, or a cohort of PD-L1-negative patients who could be discussed between the investigator and the medical monitor. There's no restriction, per se.

DR. PAPPO: For my own clarification, what is the difference between the gate 2 and 3 development, and the molecule 2 and molecule 3, is it the same thing?

DR. ROUSSEAU: Can I get maybe the trial design, the iMATRIX trial design slide, please? Yes, this one.

This is just a schematic to show that we're treating -- we are offering access at the same

sites to different molecules, currently two, so molecule 1, molecule 2. That's currently atezolizumab and cobimetinib. That's to answer your question about the different arms of the study.

Within each arm, the number of pediatric tumor types depends on the underlying biology of the tumor. For atezolizumab, we decided to have an all-comer approach, but depending on the pre-existing knowledge about a biomarker, we may restrict on a particular pathway depending on the compound. That's how the iMATRIX trial will work.

The gate, if I could get, please, the schematic on the gated approach. The first gate is PK and safety. Looking at 20 patients, at least 20 patients across tumor types, but then looking into cohorts of 10 patients per tumor type and really using the gate 2 as a predefined response rate assessment by which we will decide or not to expand into a cohort expansion.

Gate 3 is an additional set of response assessments that will define if we have reached our

phase 2 objective and if that warrants further evaluation through efficacy confirmation. We're currently before gate 2.

DR. PAPPO: I assume that you're using immune-related response criteria to assess response in these patients, or is it more a standard approach to --

DR. ROUSSEAU: No. We're using a standard approach, depending on each tumor type. So neuroblastoma includes MIBG, catecholamines, the usual response assessment for pediatric tumors, we have as exploratory endpoints and assessment based on the immune response, but not as primary endpoint.

DR. PAPPO: A final question. With a relatively crowded field of checkpoint inhibitors, how do you see this further developing in pediatrics? You have nivo, pembro, and you have evolumab.

DR. ROUSSEAU: This is exactly what we would like to avoid, is a crowded field. We've experienced that with BRAF inhibitors and would

really appreciate the support from our academy colleagues and help from health authorities in defining priorities.

I think, as you mentioned, we have several compounds of relatively the same class, and it would be great to be able to sit down at some point with the different sponsors and decide where to go in order to win rather than compete.

I think this is really a precompetitive space. As industry sponsors and particularly for our pediatric team, we need to do what's right for the kids.

This is, again, really a precompetitive area, and I think we should be able to sit down and look at the data together.

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

DR. DUNKEL: To follow up maybe on a couple of questions that Alberto just asked. Regarding the last thing you said, Raphael, about the similar agents, I thought that Genentech believes that an anti-PD-L1 agent was going to have a lower risk of

autoimmunity versus an anti-PD-1 agent.

Is that correct, and are the data bearing that out?

A second question was the question about the brain tumor. I thought that your answer was going to be that because the antibody needs to reach the tumor, if it's anti-PD-L1 agent versus an anti-PD-1 agent, that you were less optimistic that your agent would be effective for brain tumors, because it's an antibody that would have to reach the tumor cells, while nivolumab or pembrolizumab may be acting peripherally and then the cells are migrating to the brain tumor. I guess those are my two questions.

DR. ROUSSEAU: Regarding the safety profile of PD-L1 and PD-1 monoclonal antibodies, looking at the clinical data and safety data coming out from the adult studies, it doesn't seem, at this point, that we've seen a major difference in the safety profile of those compounds. That's for your first question.

For the second one, the mechanism of action

may eventually suggest that there is such a difference, but we've had some interesting surprises in some of our adult studies.

I think really the idea is to follow the science. We've seen in that particular patient with ASPS that we're not -- the drug may not cross the blood-brain barrier. As a matter of fact, it has.

I think it's important to test this in an adequate clinical trial setting. We may have some assumptions from the mechanism of action, the known mechanism of action of the drug.

Again, the immune system is something very dynamic, and so it's worth testing, under the appropriate safety concerns, supratentorial tumors, especially in children.

DR. DUNKEL: I'm sorry. Just a quick follow-up. I want to make sure I understood what you said correctly. Did you say that the data does not demonstrate decreased autoimmunity with an anti-PD-L1 versus anti-PD-1 agent?

DR. ROUSSEAU: Dr. Sandler, did you want

give some more information about the safety profile that you have observed in your adult studies?

DR. SANDLER: Hi. I'm Alan Sandler, a medical oncologist and clinical lead for the lung cancer atezolizumab program.

I can't specifically address your question with respect to head-to-head comparisons, of course, but when you look at the data as it exists today, looking at various toxicities that are known to be immune-mediated, they seem to be relatively similar in relatively similar patient populations, again, given the caveats of cross-trial comparison. Have I addressed that?

DR. PAPPO: Thank you. Dr. Armstrong?

DR. ARMSTRONG: In a pediatric trial with CTLA-4 blockade, they noted that the immune adverse effects seem to come on quickly like after the first infusion. I wanted to know if, so far, you've seen more rapid onset, different forms, and potentially the most concerning would be less reversibility of the immune adverse events in the pediatric population.

DR. ROUSSEAU: At this point in time, the safety profile in children seems to be quite similar to the adult one. We haven't seen immediate side effects that would be different in frequency than the adult ones, at least for PD-L1.

I can't speak for CTLA-4 and comparing, but at least in children, we haven't seen any safety signal of concern so far.

DR. PAPPO: Thank you. Dr. Reaman?

DR. REAMAN: Did I understand correctly that the difference with atezolizumab is that it spares the PD-L2 access? Does that sparing play any potential role in its efficacy in an antitumor setting?

DR. ROUSSEAU: This is the expected mechanism of action and the reason why we designed this monoclonal antibody to spare the PD-L2 pathway.

Again, at this stage, we haven't seen any difference in terms of safety profile with this particular characteristic.

DR. REAMAN: But in so sparing, is there any

concern that it's going to be less effective in comparison to other PD-L1 inhibitors which may also disrupt the PD-L2/PD-1 pathway access?

DR. ROUSSEAU: Again, with the caveat of not being able to perform cross-trial comparison, it seems that the efficacy of PD-L1 monoclonal antibody is quite remarkable and effective. We're not seeing anything that would suggest the contrary.

DR. REAMAN: Just another question, you mentioned that this is immunotherapy, so the responses are going to be slower, different. You did mention that you're using routine response criteria, but routine for each specific tumor, at what time, that's standardized within the gates that you've created; is that correct?

DR. ROUSSEAU: Dr. Karski, our medical monitor, pediatric oncologist on the team, will give you more details about those assessments.

DR. REAMAN: Thanks.

DR. KARSKI: I'm Erin Karski. I'm the medical monitor for the pediatric atezolizumab

study.

In response to your question about what type of monitoring are we using, for solid tumors, we're using RECIST criteria. For neuroblastoma, we're using INRC. We have Hodgkin's and non-Hodgkin's arms as well. And for those tumor types, we're using a lymphoma-specific tumor type based on a Cheson publication.

For our timing of response criteria, our first response assessment is done after 2 cycles, so that's 6 weeks. Then we continue assessments every 2 cycles so every 6 weeks.

DR. PAPPO: Thank you. Steve?

DR. DuBOIS: I had a general question about the iMATRIX and the philosophy. Just thinking, in clinical medicine, we weigh risk-benefit. Did I understand correctly that the threshold to move on to the second stage is the same regardless of the compound or potentially combination being evaluated? Wouldn't the risk weigh into what the minimum desired threshold of response would be or is it set across each agent?

DR. ROUSSEAU: At this point of time, the design of our gates is solely for single-agent assessment. I agree with you, once we go into combination, and that's the discussion we had this morning, we need to take that into account. For now, this is set assessments and set gates and criteria for each tumor type.

DR. PAPPO: Thank you. Dr. MacDonald?

DR. MacDONALD: Is the expectation that response would correlate more with relatively high PD-L1 or relatively low where you have less to overcome?

DR. ROUSSEAU: What we've seen in the adult studies, and I've shown you one of them, is that there is increased efficacy with the level of expression of PD-L1.

But we're asking that question specifically in children, so I cannot specifically answer that question for children. In adults, there is an additional benefit correlated to PD-L1 in some tumor types.

DR. MacDONALD: Just one follow-up, in

thinking about candidate combination therapies, immunotherapy-based, is there any idea that there's a shift for low PD-L1-expressing tumors that maybe they're higher in, let's say, the IDO pathway expression or some other mechanism?

DR. ROUSSEAU: Yes, so there are different hypotheses. As a pediatric immunologist, I would argue that the first element that we probably need to address is antigen presentation.

As I mentioned, PD-L1 expression may not be the most relevant biomarker at this stage. T-cell infiltrate may be also quite important. Being able to generate an immune response at the early stage of the immune activation cycle may be something of importance in children.

This is why we're really looking at our combination data with cobimetinib and atezolizumab, both to help destroy more tumor cells, but also to upregulate class 1 antigens and helps with this immune priming.

But chemotherapy, you may do that as well, or radiation therapy. It is yet too early to

decide which is going to be the best combination in children. Again, we'll look at the totality of the data, especially coming from the adult data from patients since it's very difficult to modelize, but it's too early to say.

DR. MacDONALD: Finally, in the biomarker study, are you planning to look at all aspects of immune check point system?

DR. ROUSSEAU: Dr. Hegde, did you want answer that question?

DR. HEGDE: Yes. I'll address two topics here. One is just going back to the PD-L2 expression and association with efficacy to atezolizumab.

We have looked in our adult studies, and we have, in fact, seen a positive correlation between high PD-L2 expression and efficacy to atezolizumab. We don't think that PD-L2 expression is, in some way, going to be detrimental to efficacy to an anti-PD-L1 agent.

Getting back to your question, we do have a fairly extensive biomarker strategy in the

pediatric studies. We're looking at multiple immune cell subtypes by gene expression.

In our post-dose biopsies, we're also trying to understand in patients who don't respond, for example, to monotherapy atezolizumab in these indications, what are the mechanisms associated with loss or lack of response and using those data to help us determine the best, most rational combination strategies.

As Raphael pointed out, cobimetinib is a really good example which, in fact, increases T-cell infiltration and upregulates PD-L1 expression. We do have agents in our portfolio that could dial up the expression of PD-L1 and hence, provide a good combination option and that's exactly what we're doing in our pediatric study.

DR. PAPPO: Thank you. Dr. Warren?

DR. WARREN: This is a somewhat related question, so you may want to stay up there.

(Laughter.)

DR. WARREN: It's a question regarding patient eligibility. Many of our patients are

heavily pretreated with cranial spinal radiation or transplant.

Do we know, is there any minimum immune function or arm of the immune system that needs to be intact or functioning in order for them to have a chance to respond to this compound?

DR. HEGDE: What we've learned so far is the presence of CD8 positive T-cells in the tumor microenvironment within the intraepithelial spaces of the tumor is really important to enable an effective anti-tumor immune response.

Agents that will allow us to do that effectively in tumors would be the ones that would make ideal partners for combinations, but also, as a minimum, that is what we think as really important for us to determine rather have an effective anti-tumor immune response.

DR. WARREN: I'm talking about as a single agent, is there a minimum -- patients who are on steroids but happen to be lymphopenic and got cranial spinal radiation, they would not be a good candidate, I would think, for this study.

Is there a minimum requirement for them to have a chance to respond?

DR. HEGDE: I don't think I can -- I don't have data to address this question at this moment. The minimum in the tumor that's required is the presence of T-cells.

DR. PAPPO: Thank you. Are there any additional questions for the presenters? Yes?

DR. DONOGHUE: Martha Donoghue, FDA. I was just wondering if you could comment on, based on your adult experience, what the incidence of pseudoprogression followed by prolonged disease stabilization or response has been in adults and whether you're able to draw any observations from the current pediatric study on how frequently this occurs?

DR. ROUSSEAU: Maybe Dr. Sandler will take the question on the adult pseudoprogression rate and duration of response. Then I can comment on the pediatric aspects.

DR. SANDLER: Specifically, pseudoprogression on the adult side, most of our

data is with lung, bladder, or some other solid tumors where pseudoprogression has not been seen to the same degree as seen in, say, melanoma, for example.

It has not been an issue in terms of changing absolute response rates. Response rates in the traditional RECIST criteria as compared to the immune-related RECIST criteria were quite similar in this setting.

We are looking further into that evaluation in terms of maybe there's an impact more subtle in terms of stable disease, as you mentioned, and even, dare I say, post-progression as well.

We're looking into that, don't have that data yet, but hopefully, we'd be able to present some of that data at some symposiums coming up.

DR. DONOGHUE: Thank you.

DR. ROUSSEAU: From a pediatric standpoint, we do see some patients with pseudoprogression. Again, this is too early to really make any comment on what the outcome will be.

One aspect though is -- and this is

something that we will have to discuss when we decide on the next steps or for future studies -- is that it seems that the more advanced the patients are in their disease and number of lines of treatments that they have, the least tolerance they have to pseudoprogression, advocates also for really carefully choosing patients for this type of therapies, which are quite new in the pediatric environment.

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

DR. REAMAN: I just have one question. It seems like we're sort of caught between a rock and a hard place as far as identifying the best patients for this type of therapy. Given that pediatric tumors have a low mutational burden, therefore, a few neoantigens, unless they are multiply-treated and release some of those antigens.

At the same time, their immune systems are compromised because of all the therapy they've received before this. How would you envision

ultimately developing this agent and when would it be, hypothetically, optimal to use it in frontline setting, as a relapse or salvage therapy.

Any thoughts?

DR. ROUSSEAU: All this is very premature to discuss until we see really the totality of the data of the phase 1. I would imagine, similarly to the discussion we had this morning, that quite rapidly we'd need to move in earlier lines of treatment in combination with the right backbones, chemotherapy or combining with other targeted agents.

Ultimately, my hope is that we'll be able to rapidly go into patients with lower lines of treatment to really show a clinical benefit. Yes, depending on what this first single-agent assessment will provide, hopefully by the end of this year, either we continue in single-agent if we see responses in some cohorts or rapidly move into combination.

DR. PAPPO: Thank you. Julia?

DR. GLADE BENDER: Julia Glade Bender. Hi,

Raphael. Thank you very much for your presentation.

You had mentioned that you're planning on doing standard biomarkers, but I think what we're all talking about, is there any thought to developing novel predictive biomarkers for which tumors might respond, something like an immune signature?

DR. ROUSSEAU: Dr. Hegde, did you want comment on the potential signatures?

DR. HEGDE: We do have a fairly extensive biomarker program for the pediatric program. We are working with Foundation Medicine, in fact, to develop an immune gene signature platform that, again, consists of gene signatures that represent distinct immune cell subsets.

We're also looking at common mutations within pediatric cancers and trying to incorporate the disease biology over and above the immune biology in patients.

We conduct whole exome sequencing on these patients to really understand even if they have

very few neoantigens, and are the neoantigens that are present immunogenic.

We've developed algorithms at Genentech within our bioinformatics organization to really help us understand how you define immunogenicity in these patients.

We also conduct whole exome RNA-seq in our phase 1 study to really help and understand what are the gene signatures that are associated with clinical benefit.

In our adult program, we've already seen that the presence of gamma interferon gene signature correlates very well with clinical benefit to overall survival in lung cancers, in bladder cancer as well. We're applying the same gene signature in the pediatric population as well.

We're trying to marry what we're learning in the adult indications and applying that to the peds as well.

DR. GLADE BENDER: Just as quick follow-up, could you perhaps, Raphael, explain how a predictive biomarker might be integrated into the

iMATRIX?

DR. ROUSSEAU: If we do find a biomarker signature that correlates with a clinical response, then the concept would be to enrich a cohort, that the cohort -- the specific tumor cohort using this signature.

The question is whether or not we should continue as a control to enroll some patients without that signature. Again, it's about following the science. I think if we do find a correlative signature, then we'll definitely enrich.

DR. PAPPO: Thank you. I had one additional question. Going back to the methods to evaluate response, you get a confirmation four weeks later if you demonstrate progressive disease to call it a progressive disease or it's just a one-time evaluation.

The reason why I'm asking is there's a recent paper by Jedd Wolchok in which they evaluated RECIST and the phenomenon of pseudoprogression of pembrolizumab. They claim

that you can underestimate the activity of pembrolizumab and that you can overcall progressive disease in up to 15 percent of patients by RECIST criteria, where only 5 percent of patients really develop pseudoprogression reducing the immune-related response criteria.

DR. ROUSSEAU: Yes. We do request confirmation of response. Does that answer your question?

DR. PAPPO: Yes. Any additional questions?

(No response.)

DR. PAPPO: Thank you very much.

DR. ROUSSEAU: Thank you.

DR. PAPPO: I'm going to sound like I have echolalia.

(Laughter.)

Questions to the Subcommittee and Discussion

DR. PAPPO: I know I've already said this, but there are no OPH speakers. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for

public observation, public attendees may not participate except at the specific request of the panel. We will start with the first question.

DR. DONOGHUE: Please discuss the relative expression of tumor neoantigens in specific pediatric cancers in comparison to that in adult tumors and the resulting biological rationale for evaluating atezolizumab in pediatric patients.

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

DR. WEIGEL: I would encourage the inclusion of assessing this in your study, which I think you're doing. I think we don't know. I think there's tremendous heterogeneity, and I think we don't understand right now what the expression of PD-L1 means on pediatric tumors and what the actual expression is.

I encourage the thoughtful collection of the data and analysis of the data, as well as robust biomarker development so that we can actually learn, which I would encourage you to continue to

do.

DR. PAPPO: Thank you. Yes, Steve?

DR. DuBOIS: Likewise, in terms of the tumor neoantigens, I think that's also a real gap in our knowledge. I think we understand the differences in tumor mutational burden between pediatric and adult malignancies, but whether that translates into differences in tumor neoantigens, I think, is, in my view, an open question.

DR. PAPPO: Any additional comments or questions regarding this question?

DR. ARMSTRONG: I would just echo that. I think we were very surprised in endometrial cancer to find that one microsatellite instability leads to the hundreds, if not thousands of neoantigens.

One mutation can lead to lots of neoantigens and so mutational burdens in neoantigens aren't always a straight-line correlation. I think this probably has been understudied in a lot of tumors in adults, but probably even more so in pediatric tumors so that trying to actually look at that is worthwhile.

DR. PAPPO: Any additional observations or questions?

(No response.)

DR. PAPPO: Based on what we said, I think that this drug would offer a unique opportunity to better define the mutational load of these tumors, try to correlate mutational burden with neoantigen expression, and also better clarify the role of PD-1 expression in pediatric tumors. Any additions to that?

(No response.)

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

DR. DONOGHUE: Please consider which specific pediatric cancers might be ideal candidates for evaluation of atezolizumab based upon available nonclinical and clinical data for this class of drugs and the current needs of the pediatric oncology community. Please comment regarding whether level of PD-L1 expression should be considered when selecting tumor types for future pediatric studies of atezolizumab.

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

I will start by saying that I think it's a great idea that you're not using PD-1 expression to stratify patients. A lot of other studies are doing that.

DR. ARMSTRONG: I would agree. I think that it's been a little bit disappointing in terms of what we've seen in the adult population that there's not always direct correlation.

I would say this is an exploratory endpoint that you can look at afterward when you see responses, but I would certainly not use these as criteria for eligibility at this point in time. I don't think we have enough data to narrow the focus of who we're treating yet.

DR. PAPPO: Julie?

DR. GLADE BENDER: In answer to this question, this is precisely what I think is important. We don't have a predictive biomarker,

and really any work that can be done to help us figure out which pediatric tumors would benefit from this type of therapy would be greatly appreciated.

DR. PAPPO: Yes, Brenda?

DR. WEIGEL: I would also encourage thoughtful consideration of sites of tumors, especially CNS tumors, for the assessment of these agents. It's a very special site, and we have to be very careful not exclude those patients, but thoughtfully consider ways of including them in the assessment of this type of a drug, and also consider, I think, some of the points that have been brought up as baseline immune status, lymphocyte counts, as well as tumor burden with also sites of disease, things like effusions, et cetera and really thoughtfully consider how that may impact the assessment of the drug.

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

DR. MacDONALD: I would also encourage, because of the lack of correlation with expression

response, that alternative mechanisms of immune check point evasion are looked into, whether internally or collaboration like IDO pathway or something of that nature.

DR. PAPPO: Any other comments?

(No response.)

DR. PAPPO: Again, this trial would offer a unique opportunity to better define which are really the tumors that could benefit from this therapy that gives the overall answers that we really do not know.

It also offers the opportunity to better define potential predictive biomarkers for pediatric tumors and better identify which tumors would benefit from this therapy.

We also believe that other endpoints should include evaluation of the immune status of patients that go on trial, including tumor burden and absolute lymphocyte count.

This drug also would offer an opportunity to better define the mechanisms of evasion to activity of PD-1 inhibitors.

I think everybody agrees that it's a very good idea not to stratify patients by PD-1 expression in this trial.

Anything else? Yes, Dr. Reaman?

DR. REAMAN: I think in addition to just looking at absolute lymphocyte count, we hear the concern about the steroid use and whether that impacts. But are there adult data to suggest that that really does happen?

I think looking at other immunosuppressive therapies, extent of cranial spinal radiation, or radiation of the pelvis, use of steroids, and use of other immunomodulatory drugs that might impact the mechanism of action should be evaluated, too.

DR. PAPPO: Thank you. If there are no additional comments or questions, we will move on to question number 3.

DR. DONOGHUE: Please consider the ongoing pediatric study and provide an opinion regarding the overall study design, including the patient population eligible for enrollment and the ability of a gated design to identify the tumor types that

should be further studied.

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

DR. ADAMSON: I think the design is on target. Let me try to parse the question.

We've discussed this before with the team. As Raphael mentioned, this is a classic phase 1 two-stage Simon design phase 2 trial. That's how we've historically always developed drugs, certainly with cancer, multiple strata for phase 2.

I think the only concern I would have with the two stages is whether we set the bar too high on the first stage. If it's really going to be 3 responses out of 10 before going on -- I think it was 2 or 3. That's a pretty high bar for a first stage in many cancers.

I would have some concern, especially with the lack of biomarkers and looking for biomarkers. For us, if we were to see 2 out of 10 responses to shut it down at that point, I think, might not be

the right threshold, so consideration to lowering the threshold to go from stage 1 to stage 2.

I do think for this drug, though, what is a broad-based approach to pediatric tumors makes a lot of sense. We don't know what the predictive markers are going to be.

This is obviously a highly active class of drugs for certain adult cancers, and we should not presume we know precisely which tumors it may or may not work in.

I think the overall approach of looking at multiple disease strata, looking for those signals, and, ideally, if you see those signals, to run with those signals and really do a deep dive when they're there is something I would support.

DR. PAPPO: Dr. Neville?

DR. NEVILLE: Just to build on what Dr. Adamson is saying, I would also encourage you to move quickly to combination studies. So you now have this the phase 1 safety data. But this class of drugs, I think, in particular, that is a very high bar because of how the drug works. I would

encourage you not to throw the drug away before you get combination studies.

To his earlier point, there is still quite a lag in drug development in rare diseases in pediatrics, we all know that. To start getting efficacy, we should hurry up with the combination studies.

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

DR. BROWN: One of the things that has just struck me is in the adult setting, there appears to be at least a reasonable correlation between histology of the tumor and response.

I just am thinking that another hypothesis that might be at work here is that it may not be as related to tumor type in pediatrics. It may be more related to something about the immune competence of the patient, age at which they're being treated, et cetera.

One might want to consider being more of a lumper than a splitter in terms of the design of the study and not assuming that histology is going to be driving response to the same degree in

pediatrics as is true in adults.

DR. PAPPO: Thank you very much.

Dr. Warren?

DR. WARREN: In regard to the response criteria, as well as for some of the adult trials where we expect to see pseudoprogression, we allow for percent increase in the tumor size in the MRI scans before taking a patient off of the study. I think it's important to build in criteria to take patients off.

In that regard, I also think it's important to collect data on quality of life or other clinical outcome measures to see actually if a patient is suffering while they have long-term stable disease and see if it really impacts on their quality of life.

DR. PAPPO: Thank you very much. Anybody else?

(No response.)

DR. PAPPO: We'll try to sum up this. Overall, the committee feels that the study design is on target. It's a classic phase 1/2. One of

the concerns is whether the bar has been set too high and just consider bringing down your response rate to a more reasonable one in order to further then do a deeper dive if you see a specific signal in a specific subset of patients.

Also, consider combination studies, and those should be done relatively quickly once you've identified a dose and a subset of patients that may benefit from this drug.

Also, it may be that correlation of histology and response may not be a very clear -- there might not be a very clear correlation between histology and response in pediatric tumors. Therefore, you should explore immunecompetence, age and other factors to better assess the reason for the response in these patients.

Finally, try to expand some of your objectives. Despite the fact that patients might progress, try to collect data on quality of life and other outcomes to better assess the potential benefit of this drug in pediatric patients.

Anything else?

(No response.)

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

DR. DONOGHUE: Please consider the toxicity profile of atezolizumab in adults and discuss whether there are unique safety concerns related to potential short and long-term toxicities from the use of PD-L1 inhibitors in pediatric patients. Also, discuss potential ways to mitigate these risks.

DR. PAPPO: Based on the data that has been presented, it appears to have a very similar toxicity profile as other PD-1 inhibitors. I assume that we would expect a variety of side effects that would occur at different times, the rash, then the diarrhea, then the liver function test, and then the endocrinopathies. I assume that all of this is being monitored relatively closely in the protocol.

I don't have an answer as to potential ways to mitigate these risks other than close

observation and try to implement the therapies that are necessary to deal with these side effects in a very timely fashion.

Dr. Adamson?

DR. ADAMSON: I would echo that, Alberto. I think if we're fortunate enough to see a strong efficacy signal, that's when we'll be able to get into the long-term.

I don't think we're going to be able to predict what impact this may have. As far as on autoimmunity, I would love to see what data there are in adults, but I don't think that necessarily will extrapolate down into the pediatric population.

I don't see any red flags waving as far as why we would not proceed with developing this and seeing if we can find a signal that will move it upfront that eventually would allow us to look at some long-term issues.

DR. PAPPO: Thank you very much. Dr. Glade Bender? Julie?

DR. GLADE BENDER: I do think, though,

vis-à-vis the short-term toxicities, we could all use some better guidance on the use of steroids, like Dr. Reaman had mentioned.

I think a lot of protocols frown upon the use of steroids, and so you feel like you have to take the patient off study if they don't recover quite quickly.

If we could have a better understanding about how to use steroid if we do run into one of these side effects and whether we could keep the child on trial, that would be very helpful.

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

DR. RAETZ: Just one comment about the AYA population, it doesn't sound like from what's been discussed that there would be predicted to be a difference in the toxicity profile that's age-related. But if there is a signal that there's perhaps more toxicity or different toxicities in that population, you'd hate for that to influence your decision for the pediatric patients.

If you'd see that, you might want to limit the number of AYA patients per cohort or if there's

any concerns along those lines.

DR. PAPPO: Any additional comments regarding this question or questions?

(No response.)

DR. PAPPO: I believe that based on the data that has been presented, there are no significant concerns as unique toxicities that may be seen in pediatric patients.

We believe that it's reasonable to proceed with the development of the drug as you have explained it.

We would very much appreciate a better guidance on how to mitigate some of the side effects, specifically when to introduce steroids to try to keep the patient on protocol, especially if there appears to be benefit from drug and, also, to be able to identify early some signals of concern in selected patients.

Any additional comments or anything?

(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 can be recycled. Thank you very much. We'll see you all tomorrow.

(Whereupon, at 2:44 p.m., the afternoon session was adjourned.)