FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE (pedsODAC)

Afternoon Session

Thursday, June 20, 2018

12:45 p.m. to 2:28 p.m.

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

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

(12:45 p.m.)

Call to Order

Introduction of Committee

DR. PAPPO: Good afternoon. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Amanda Turney. If you are present, please stand.

My name is Alberto Pappo. I'm a pediatric oncologist, and I will be chairing today's meeting. I will now call the afternoon session of the Pediatric Oncology Subcommittee of the Oncology Drugs Advisory Committee to order. We'll start by going around the table and introducing ourselves. We will start with the FDA to my left and go around the table.

DR. REAMAN: Gregory Reaman, FDA.

DR. CASAK: Sandra Casak, FDA.

DR. DREZNER: Nicole Drezner, FDA.

DR. SINGH: Sonia Singh, FDA.

DR. KAMANI: Naynesh Kamani, pediatric immunologist and bone marrow transplant physician, Children's National Medical Center, Washington.

DR. ANGIOLILLO: Anne Angiolillo from Children's National Medical Center.

DR. LAETSCH: Theodore Laetsch, pediatric oncologist at UT Southwestern.

DR. DuBOIS: Steve DuBois, Dana-Farber, Boston Children's.

DR. HOTAKI: Lauren Hotaki, designated federal officer.

DR. RINI: Brian Rini. I'm an adult GU medical oncologist at Cleveland Clinic.

MS. LUDWINSKI: Donna Ludwinski, patient advocate.

DR. BENDER: Julia Glade Bender. I'm a pediatric oncologist at Memorial Sloan Kettering.

DR. SMITH: Malcolm Smith, the National Cancer Institute

DR. SHAH: Nirali Shah, Pediatric Oncology Branch, National Cancer Institute and pediatric oncologist.

DR. MORROW: P.K. I'm a medical oncologist employed by Amgen, and I'm the industry rep.

DR. PAPPO: Thank you very much.

Courtney, can you introduce yourself?

MS. PREUSSE: Courtney Preusse, consumer rep.

DR. PAPPO: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the

meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Lauren?

Conflict of Interest Statement

DR. HOTAKI: The Food and Drug Administration is convening today's meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

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

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

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

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

their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

During the afternoon session, information will be presented to gauge investigator interest in exploring potential pediatric development plans for a product in 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 this product 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 is ONC201, presentation by Oncoceutics, Inc. This is a particular matters meeting during which specific matters related to pediatric development plans for

ONC201 will be discussed. Based on today's 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. Theodore Laetsch.

Dr. Laetsch's waiver involves his employer's research contract with Pfizer through a subcontract with the Children's Oncology Group for which the study finding is between zero and $50,000 per year. The waiver allows Dr. Laetsch to participate in today's deliberations.

FDA's reasons for issuing the waiver is described in the waiver document, which are posted on FDA's website. Copies of the waiver may also be obtained by submitting a written request 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.

Dr. Ira Dunkel has been recused from participating in this session of the meeting.

To ensure transparency, we encourage all standing members and temporary voting members to disclose any public statements 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 nonvoting industry representative acting on behalf of regulated industry. Dr. Morrow's role in 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 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, Lauren.

We will now proceed with an FDA introductory remark from Dr. Greg Reaman.

FDA Introductory Remarks - Gregory Reaman

DR. REAMAN: Just briefly, this afternoon session is distinct from this morning's session, which really focused on one of the legislative initiatives and amendments to that piece of legislation, the Pediatric Research Equity Act.

This afternoon, we'll be utilizing the other piece of legislation, which has really been the only legislative option available for pediatric cancer drug development, the Best Pharmaceuticals for Children Act.

I'll remind you that BPCA is a voluntary program. It's a voluntary program for industry to conduct studies sometimes in a different indication than that for which the drug is originally being developed for adults historically, and the development is done through a process known as a

written request. The agency issues a written request to the sponsors, generally after we're asked to do so, through a proposed pediatric study request. Sometimes, however, we issue them on our own.

The written request details, the specific studies to be included as far as patient population study designs and specific timelines. If the requirements of the written requests are met, then the sponsor is eligible to receive six months additional exclusivity or patent life extension on the product.

It has been extremely helpful to childhood cancer drug development. However, historically, we've issued written requests years after a drug has been approved for the adult indication. In attempt to maximally leverage our authority the last few years, we've been inviting companies to come to the pediatric subcommittee meetings, present their product and potential pediatric development plans to gauge investigator interest in whether or not a written request is feasible and

appropriate.

So we're here, really, today to talk about exactly that, to hear about the mechanism of action, the clinical development to date, and what potential indications or applications to the pediatric cancer population this product might have.

DR. PAPPO: Thank you, Dr. Reaman.

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

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

outcome of the meeting.

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

We will now proceed with Oncoceutics' presentation.

(Pause.)

Industry Presentation - Wolfgang Oster

DR. OSTER: Thank you, Dr. Pappo, Dr. Reaman, and members of the pediatric subcommittee of ODAC, and members of the FDA, I'm Wolfgang Oster with Oncoceutics. On behalf of the company, we are grateful for the invitation to present here today.

ONC201 is the lead compound of a new chemical class that we have created called the imipridones. This family is comprised of chemical analogs of ONC201 that share a novel pharmaco

for [indiscernible] and represent an opportunity to target G protein-coupled receptors, abbreviated GPCRs, for their use in oncology.

Fewer than a handful of cancer drugs target these receptors, and none of them are used in neuro-oncology. One of the reasons for this paucity is the need for selective effects on malignant versus normal cells, which require drugs that bind to GPCRs with a very high degree of specificity.

GPCRs are the largest class of membrane receptors in humans. These receptors are rational targets for dysregulation by malignant cells, as a single receptor can command a vast array of pro-survival and stress-response signaling pathways that are depicted in the cartoon in the center of this slide.

Despite the dysregulation of many of these receptors in cancer, illustrated by gene expression in the heat map on the right side, GPCR targeting agents have been underexploited in oncology. Dopamine receptor 2, or DRD2, is a member of the

GPCR super family that exhorts multiple functions, including a major role in the progression of glioma. The challenge was to find a compound that specifically antagonizes DRD2 to accomplish selective antitumor activity. Our lead compound ONC201 is the first highly selective DRD2 antagonist for the use in oncology.

One of the focus areas for the development of ONC201 are patients with a specific form of high-grade glioma that harbor a mutation, referred to as H3 K27M. Many of the patients are children, and the mutation is particularly common in midline structures of the brain such as the pons. This form of disease is called diffuse intrinsic pontine glioma or DIPG.

DIPG is an ultra rare disease with an incidence of approximately 300 patients annually in the United States, mostly young adults and children. DIPG is immediately life threatening. It meets the criteria of a serious disease. No effective therapy exists. No response criteria have been established. No drug has ever been

approved by the FDA. Radiation is used with only palliative intent. Overall survival has stagnated at a medium of 8 to 12 months after diagnosis and at a 2-year survival rate that is uniformly low at around 5 percent.

We appreciate the opportunity to discuss some of the challenges that we are facing with our new therapy developed for this disease. This slide shows you the agenda and the speakers. We also have a group of experts who have worked with us to plan our development, some of whom are with us here today and are prepared to participate in the discussions.

You will note that several of the clinical data presented today are from our adult program where the efficacy signal for this disease was first detected. Josh Allen, who leads our R&D program, will walk you now through the receptive pharmacology, which is particularly important to understand our drug, of ONC201 and DRD2, as well as the specifics of the mutation that we target. The mutation is on the list of relevant molecular

targets outlined by Pediatric ODAC.

Josh?

Industry Presentation - Joshua Allen

DR. ALLEN: Thank you, Wolfgang.

Dopamine receptors are categorized into two subfamilies with opposing downstream consequences that are important for normal physiological equilibrium. In oncology, cancer cells hijack this pathway in a highly selective manner by overexpressing DRD2 rather than other family members, as you can see in the RTPCR analyses shown in the center of the slide.

Selective DRD2 overexpression in its critical role in driving tumor growth has been studied in many types of cancer, most extensively in high-grade gliomas, as demonstrated on the right in glioblastoma.

ONC201 is the first bitopic DRD2 antagonist for oncology. The term bitopic refers to the requirement of orthosteric and allosteric residues in antagonism of the receptor. The required orthosteric amino acids are shown in the crystal

structure on the left in green spheres, which allows ONC201 to compete with the native ligand dopamine. There are also allosteric amino acids required by ONC201, some of which are only conserved in DRD2 and sometimes DRD3, as depicted by different color spheres.

These residues are key for the selectivity of ONC201 for these two receptors over other dopamine receptors, as seen on the right. This selectivity is critical for the safety and efficacy of ONC201 that you will see reflected in the clinical data presented by subsequent speakers.

In addition, the lower-right panel shows you the unique functional impact of this bitopic interaction with DRD2 on dose-response assays with dopamine. You can see the right shift in IC50 due to competitive inhibition by ONC201, whereas the required allosteric residues confer noncompetitive inhibition of the receptor that results in a downshift of the curve. This downshift indicates the unique ability of ONC201 to curtail the maximum stimulatory effect that dopamine can have on this

receptor, which may be an important feature in dopamine-rich microenvironments present in some tumors.

ONC201 penetrates the blood-brain barrier and achieves biologically active central nervous system concentrations, as you can see on the left in rodents using pharmacodynamic and LCMS assays. These features culminate in antitumor efficacy for high-grade gliomas, as shown on the right, where mice with orthotopic glioblastoma exhibited significant tumor regressions and a doubling of their survival in response to a single oral dose of ONC201.

We have seen translation of ONC201's preclinical profile to humans. Here you can see the procedural outline and results from 6 patients who received ONC201 prior to resection of their recurrent glioblastoma. In the upper right, ONC201 achieves intratumoral concentrations at 24 hours post-dose that exceed therapeutic thresholds defined in neurosphere glioblastoma cultures. In the lower right panel, you can see that this

exposure is sufficient to elicit an intratumoral pharmacodynamic response involving targeted pathways and apoptosis in a molecular subset of these patients.

H3 K27M mutant glioma is a molecular subset of high-grade gliomas that exhibit pronounced sensitivity to ONC201. As summarized in the cartoon on the left, H3 K27M is an oncohistone mutation that directly inhibits the PRC2 to methylation complex, generally leading to a global histone hypermethylation phenotype. The consequence is epigenetic dysregulation of the expression of many genes associated with cancer, including dopamine receptors as shown here.

Gliomas with this mutation are responsive to ONC201 in preclinical models, as shown on the right in a genetically engineered mouse model of H3 K27M mutant DIPG, developed by the lab of Carl Koschmann at the University of Michigan.

I will now turn the presentation over to Dr. Patrick Wen, director of neuro-oncology at the Dana-Farber Cancer Institute and the physician who

treated the first H3 K27M mutant glioma patient with ONC201.

Industry Presentation - Patrick Wen

DR. WEN: Thank you, Josh.

The first phase 2 clinical trial of ONC201 was conducted at Dana-Farber and MGH with ONC201 administered at 625 milligrams every 3 weeks to adults with recurrent IDH wild-type glioblastoma. The first arm of this trial enrolled 17 patients with several poor prognostic factors. The median life expectancy for this group of heavily pretreated patients, the majority of whom were MGMT unmethylated, would be in the order of 5 to 7 months.

The median survival in this molecularly and selected patient group treated with ONC201 was 9.7 months. Based on the excellent safety profile and the potential efficacy of the drug, we shortened the administration interval to once weekly at the same dose. The efficacy and safety results of this weekly dosing cohort was comparable to the first cohort.

These clinical outcomes plus the intratumoral pharmacodynamics described earlier warranted further investigation in glioblastoma. Early on in the trial, an exceptional response was observed in one patient with H3 K27M mutant glioma, and the preclinical findings prompted further clinical evaluation of this molecular subset of high-grade glioma.

This patient was a young woman who progressed on temozolomide and radiation therapy. She began treatment with single-agent ONC201 at the age of 22. As you can see from the MRI, her primary thalamic lesion completely regressed, and her secondary lesion in the parietal lobe has decreased in size. She resumed college while working a part-time job, in part, thanks to the ease of the infrequent oral schedule and the lack of side effects. Recently, she graduated.

H3 K27M glioma is a distinct form of grade 4 glioma that was first codified by the 2016 WHO criteria. As I'm sure you're aware, of all the subtypes of glioblastoma, this is the worst. I'm

reporting 15 adult patients who met stringent prespecified criteria to isolate the effect of single-agent ONC201 in this subgroup. All of these patients shared the following characteristics. They were older than 16 years of age; confirmed H3 K27M mutation in their CLIA lab; recurrent disease by RANO criteria; more than 3 months from completion of radiation; and primary disease not involving the pons and spine.

The patients are pulled from 2 clinical studies across 5 clinical sites, and one patient who is treated under an expanded access protocol. This table summarizes the demographics of these patients who are young relative to glioblastoma with primary tumors located throughout the midline.

Unlike other high-grade gliomas, midline gliomas often exhibit areas on MRI that do not contrast enhanced with gadolinium and some areas that do. Whereas response criteria have not been developed for midline gliomas, RANO criteria, developed separately for contrast enhancing and non-contrast enhancing disease, can be utilized

here.

Overall response rate by blinded independent review was performed. So far, best response by RANO high-grade glioma, assessing contrast enhancing disease, is at least 27 percent. Best response by RANO low-grade glioma criteria, assessing non-contrast enhancing disease, is at least 36 percent.

Best response, counting a response by either criteria, is at least 47 percent with 2 complete responses. The lower 95 percent confidence interval limit is currently 21 percent. Six patients remain on treatment, and therefore best response could improve with further maturation.

Other than these results with ONC201, I'm not aware of any objective responses reported in this setting. An independently conducted systematic literature search confirmed no objective responses have ever been reported in adult recurrent midline gliomas. Also remarkable is the disease control rate of 80 percent, as even disease stabilization can be viewed as a disease treatment

success in this disease.

The waterfall plot shows 6 patients remain on study, including some patients with regressions categorized as stable disease, and therefore the depth of responses may increase with further readout. In addition, there is one patient not included in this analysis who had 3 subcentimeter malignant lesions at baseline that were not measurable by RANO criteria. However, all three target lesions regressed completely on the first 8-week MRI and remain durable for more than a year.

The spider plot shows the durability of regressions that bodes well for the veracity of these responses and explains the translation of these effects into a survival benefit. Median onset of response was 2.1 months with a range of 1.6 to 3.7 months. Median duration of response has not been reached with a median follow-up of 1.9 months; 8 out of 15 patients are still alive, and thus, median OS has not been reached. The survival date is still maturing with a median follow-up of 7.5 months.

One striking feature of the drug is that it is very well tolerated with no grade 3 or 4 adverse events or serious adverse events attributed to the drug. No patient has discontinued therapy due to drug related toxicity. The safety profile is consistent with that observed in more than 350 patients enrolled across 13 clinical trials and expanded access spanning a range of advanced malignancies, as regularly reviewed by independent data safety monitoring boards. Overall, the quality of life of patients has been excellent, better than almost any other targeted therapy I've ever worked with.

In addition to the easy administration schedule and benign safety profile, several of these patients have reported resolution of disease-associated symptoms. Some of them have reported their experience to investigators, and we're systematizing the capture of this information with suitable modules.

Here you can see the rapid response in a patient with recurrent disease located in the

cerebellum that has deepened over time and has resulted in a normalization of several neurologic deficits caused by the tumor. We are compelled by the concordance for the range of endpoints affected by ONC201, including response rate, durability of response, neurologic improvements, and other clinical benefits in patients like this.

We will now turn over the presentation to Dr. Sabine Mueller from UCSF.

Industry Presentation - Sabine Mueller

DR. MUELLER: Thank you, Patrick.

The pediatric oncology community has been unsuccessfully searching for decades for therapies to help children with midline gliomas. The relatively recent discovery of the molecular nature of these tumors has brought a fresh sense of hope to the community. Given the activity of ONC201 in adult patients with midline gliomas that have the H3 K27M mutation that is also present in the majority of pediatric midline gliomas, we have been eager to evaluate the agent.

In the first phase 1 study, ONC201 was

administered as a single agent in previously treated H3 K27M mutant glioma or concurrently with radiation therapy in patients with newly diagnosed DIPG. To complement standard secondary endpoints, a cranial nerve palsy score was developed as shown here. Patients treated with ONC201 experienced significant improvement of their cranial nerve palsy.

There are 5 arms in this clinical trial. Each has its own objective. Arm A and E are establishing the safety of ONC201 as a single agent administered as an oral capsule or as an oral formulation to post-radiation H3 K27M glioma patients. Arm B established the safety of ONC201 in combination with radiation for newly diagnosed DIPG patients. Arm C evaluates intratumoral drug levels and PD effects of ONC201, and Arm D evaluates circulating tumor DNA in the cerebral spinal fluid under ONC201 therapy.

The results that I will show you predominantly are from patients enrolled in Arm A that involve single-agent dose escalation in

post-radiation H3 K27M glioma patients, which is complete. The safety results for the 21 evaluable patients treated in arm A are consistent with a benign safety profile observed in adults.

The adult recommended phase 2 of 625 milligrams once per week was scaled to body weight bins to pediatric patients. No patient in this arm experienced any drug related grade 3/4 toxicities. The majority of the low-grade toxicities attributed as possibly related to study drug were nausea and headache that are also commonly associated with the underlying disease.

A preliminary pharmacokinetic analysis shows that profiles appear to be consistent with those observed in adults; low micromolar peak concentration around 2 hours and a terminal half-life of around 7 hours. The plasma concentrations appeared relative consistent across weight bins, and in the therapeutic range defined in DIPG in vitro model.

All patients enrolled to the phase 1 study had H3 K27M mutant glioma and/or DIPG. However,

there was a variability in treatment settings and imaging features. While acceptable for the primary endpoint of safety, this setting does confound interpretation of efficacy results. Nevertheless, substantial and durable tumor regressions have been observed in some patients while on treatment with kinetics that are atypical for the disease course.

On the left is a patient with a large thalamic tumor exhibiting the H3 K27M mutation who received single-agent ONC201 after radiation. The tumor exhibited roughly 75 percent regression relative to the post-radiation tumor size, and this patient continues on therapy to date.

On the right is another patient who has shown a dramatic reduction in her circulating tumor DNA in the CSF associated with a greater than 50 percent reduction of tumor size. Going forward, we intend to confirm the utility of ONC201 in pediatric patients with progressive H3 K27M mutant glioma as described for adult patients.

While radiographic evaluations are challenging in DIPG with available criteria due to

its diffuse imaging appearance and a minimal contrast enhancement, newly diagnosed DIPG represents the group in the study where overall survival is a widely accepted endpoint. Moreover, results from a multitude of clinical studies showed that overall survival is superimposable with little variability, independent of treatment, allowing a direct comparison to outcomes generated with ONC201.

Shown here are 13 DIPG patients who received single-agent ONC201 after completion of radiation; 6 patients had sequencing available; 5 patients had H3.3; 1 patient had H3.1 mutation; 6 other patients were identified as H3 K27M by immunohistochemistry, and 1 patient had not been profiled.

Please note that we have chosen to analyze progression-free survival and overall survival from time of diagnosis, not from the time of initiating ONC201. We did this to establish a common time point to enable comparison to historical controls.

As you can see, median overall survival has not been reached with a median follow-up of 13.2

months. Median overall survival is typically 8 to 12 months after diagnosis. The historical overall survival at 12 months rate when measured from diagnosis is about 40 percent for DIPG patients, and therefore we observed overall survival rate at 12 months, where 69 percent is encouraging, especially since only 2 subjects in this cohort were re-irradiated. If this improvement in survival beyond historical outcome is confirmed, this would be a first in our field.

Shown here are ongoing and planned clinical trials with ONC201 in pediatric high-grade gliomas that efficacy endpoints that could be suitable for approval. The ongoing pediatric trial will continue to accrue newly diagnosed DIPG patients and will evaluate overall survival.

In addition, the study will be amended to include a dedicated expansion for progressing non-DIPG H3 K27M mutant glioma patients that will evaluate response rate. There's also an intermediate size expanded access protocol for DIPG and H3 K27M mutant glioma patients who cannot

access ongoing clinical trials with ONC201. This protocol is conducted under Oncoceutics IND and collects information that is similar to the clinical trials.

In addition, there are several studies in development for newly diagnosed glioma patients. One international trial under development is a joint effort between NRG and COG to evaluate ONC201 concurrent with radiation and post-radiation newly diagnosed patients with DIPG to confirm findings in the ongoing trial and/or H3 K27M mutant glioma. The primary endpoint of overall survival will be evaluated for DIPG and non-DIPG in separate arms.

In Europe, ONC201 is being incorporated into the next version of a BIOMEDE clinical trial that will enroll diffuse midline glioma patient with H3 K27M or H3 K27M trimethyl loss. Another trial in development is one that I'm designing through PNOC that will evaluate pharmacodynamic-based endpoints for ONC201 in midline glioma patients as a single agent and combination, agnostic to the H3 K27M mutation.

We believe that this program broadly evaluates the profile of ONC201 in patients with H3 K27M mutant glioma and/or midline gliomas across age groups, different lines of treatment, and with multiple endpoints. We look forward to working with this committee and the FDA to best utilize emerging data to introduce the drug into medical practice for patients with this rare and lethal disease.

Thank you for attention, and thank you to the patients and their families who participate in our studies.

Clarifying Questions

DR. PAPPO: Now we're going to proceed with clarifying questions. Please state your name to the record if you speak, and if you can please direct questions to a specific presenter, please.

DR. KAMANI: Naynesh Kamani. What's the rationale for the weekly dosing if the half-life is 8 hours? Is that related to fears of toxicity or is there some other reason?

DR. OSTER: a very good question. Thanks

very much for that. Let me introduce Marty Stogniew, our chief development officer, who's going to address this question.

DR. STOGNIEW: The schedule was not selected due to toxicity. What basically we did, we did a lot of preclinical work, and found out that there is a large disconnect between the PK and the PD. In adults, the PK is approximately 10 hours, but the PD lasts for weeks. What we did was we did studies that showed that, actually, no more than weekly dosing improved efficacy, and doses above the equivalent of 125 milligrams in humans had no improved efficacy.

We've now confirmed this the intratumoral PD and concentrations that Dr. Wen showed, and we now see efficacy in patients given weekly or every 3 weeks. If you'd like, I can show you the data, but that's basically the overview. Thank you.

DR. PAPPO: I had a couple of questions. It's still unclear to me what is the relationship between the dopamine receptor and this mutation? Does this mutation upregulate the dopamine

receptor, or what is it exactly that is the mechanism that's allowing this drug to work? Then I'll get to my second question.

DR. OSTER: Very good question. Thank you, Dr. Pappo.

DR. ALLEN: Thank you. To be clear, the molecule is a DRD2 antagonist, so what we're looking for are tumor cells that have dysregulated this pathway in a way that is wired to be addicted. So we're looking for cells that are overexpressed DRD2 and underexpressed DRD5. We believe that the H3 K27M mutation is one way to do this. I just want to be clear that there's no reason to believe the activity would be restricted only to that mutation.

In terms of the specifics of how the K27M mutation connects to the dopamine receptor expression, would you like me to elaborate more on that with data?

DR. PAPPO: [Inaudible - off mic].

DR. ALLEN: Okay. Great.

DR. PAPPO: Thank you.

DR. ALLEN: Slide up.

DR. HOTAKI: Just for the record, can you introduce yourself for the transcriber?

DR. ALLEN: I apologize. Josh Allen, SBP of our research and development at Oncoceutics.

The H3 K27M mutation, like I mentioned in the main presentation, is an oncohistone mutation. What's happening here is K27M, that lysine is normally trimethylated or can undergo other post-translational modifications. The trimethyl mark at this site is generally an epigenetic repressive mark, so when it's present and sticking to a gene, it's generally keeping the expression low.

If we look at normal neural stem cells at the top of this slide, what you see is there's an association of H3 K27 trimethyl on the DRD2 gene as it compares to the control shown there. When you have the H3 K27M mutation introduced, that substitution turns this histone into a physiological dominant negative inhibitor of the PRC2 methylation complex. So basically you see K27

trimethyl go away, and that's exactly what you see in many places, including the DRD2 gene. Those are the tracks shown at the bottom.

The net consequence of that is shown at the bottom of the slide. If you take a look at RNA-seq experiments, looking at dopamine receptor expression, for gliomas that have this mutation versus those that do not, you can see this at the bottom.

On the left-hand side, you can see H3 K27M gliomas have higher expression of DRD2 because that epigenetic repressive mechanism is being released. Then you see the consequence of that in the cell viability assays on the right, where the cells with the mutation exhibit both a more complete response and a lower IC50.

DR. PAPPO: Thank you very much. I had another very quick question. I know that numbers of patients is relatively limited, but have you been able to dissect out subgroups that appeared to benefit from this drug? I saw, for example, in the adult studies that most of the ones that benefited

gad thalamic primaries, where as the DIPGs did not appear to have such dramatic responses.

There's also some data, at least in pediatrics, that there are certain small subgroups of patients with DIPG, those that are younger that have necrosis, et cetera, that appeared to have long-term survival compared to others. I don't know if you've had a chance to look at that or it's just the numbers are too small to make any specific conclusions.

DR. OSTER: We have several answers to this question, but obviously the intention was here to create a patient population, which is homogeneous enough to allow an interpretation. That's the bottom line why we did this. We actually predefined or prespecified criteria to select this patient population before we did this analysis.

Josh, do you want to go?

DR. ALLEN: Yes, absolutely. I think we have a keen eye on this question. There are obviously different elements of heterogeneity. You mentioned age and location, and we're obviously

interested in different isoforms as well, 3.1 versus 3.3. We see in the preclinical models, there's no clear defining co-varying factor that dictates response. We're keeping our eye on all those factors in the clinic right now, and just need more patients and more readout to be able to adequately perform those analyses.

DR. DuBOIS: I wonder if you were surprised by the lack of neuropsychiatric toxicity, based on the role of dopamine in normal physiology.

DR. OSTER: Very good question. Safety slides; slide up.

This is the profile, basically, of our safety reports. You see a lot of zeros for grade 3's and 4's. When you actually go further into the details, you hardly find any side effect that is possibly or probably related. We don't have a single one, except a mild allergic reaction that was reported as related.

This is a remarkable safety profile, and we have been trying to understand this ourselves, because if you go to the next slide, when you knock

out DRD2, you do get side effects. You do get very significant side effects, locomotor deficits and so on, as shown here in an animal study. But that's not what we do. We do not knock out DRD2.

Let's go to the next slide. What we do is actually ONC201 binds to the receptor, and it has a very unique receptor pharmacology. It has a very long on rate and a very short off rate. That is a typical feature for modern anti-psychotics. They have a much reduced safety profile. That's basically what we mimic. The key element here is that, basically, we really don't knock out DRD2 function. We bind to it briefly, induce prolonged pharmacodynamic effect, which is exactly what we want in terms of induction of apoptosis.

DR. DuBOIS: If I may ask a second question, are there data in other pediatric cancers where there's this imbalance of dopamine receptors? What comes to mind is a disease of interest for me, neuroblastoma, which is known to overexpress catecholamine receptors. I wonder if you've looked at other pediatric tumors.

DR. ALLEN: Yes. It's a great question. We're compelled by what we're seeing in this current population, but we're obviously excited and compelled to see what more we can do with this drug and who else we can bring it to. To that end, most of the studies that have been performed historically with the drug have been focused on adult cancers.

However, we have begun, especially with the data that you've seen, to initiate collaborations with people to further explore where the dopamine pathway is dysregulated in pediatric oncology and validate that this agent is really active in in vitro and in vivo models, hopefully to eventually lead to clinical studies.

Slide up. So to this end, we took a lot of the data that you've seen today and submitted an application to the Pediatric Preclinical Testing Consortium. What we did is share some of our thoughts, not only the data but the predictive biomarker signatures that we've trained in vitro and validated in our adult clinical studies to see

if some of that dysregulation is happening in some of the available data sets in pediatric oncology.

We do see elements of the dopamine pathway being dysregulated. You've already named neuroblastoma. We certainly see that in bioinformatic analyses. There are several other tumor types listed up there on that slide. So we're encouraged, and we're working with this group to validate if indeed the drug could have potential in that setting.

DR. LAETSCH: Ted Laetsch. I was going to ask as similar question to what Dr. Pappo asked, but around mechanisms of resistance. When I look at the data, it seems like there are two cohorts of patients within the H3 K27 and a group of patients who seem to have pretty impressive responses, that seem to be durable in your early data and another group of patients that have primary progression.

Do you have a sense of other biomarkers that can be used to distinguish those groups?

DR. ALLEN: We certainly do. I would acknowledge that the kind of patient population

we're working in right now with these midline gliomas, we do have challenges with how we evaluate them. Depending on where the tumor is, they can image differently than other ones.

But you're right. And when we look at the data, there's certainly a heterogeneity of responses. There almost always is. We've looked for mechanisms of resistance, and that's divided into acquired resistance and innate resistance. So we have some data to share with you if you'd like.

Slide up. So what we did in the lab was this is not a study, actually, that's specific to high-grade gliomas, but we took solid tumor models that were sensitive to ONC201 and basically forced resistance in the lab by steadily increasing the concentrations. This was right around the same time we uncovered the DRD2 binding target of the molecule, and it was interesting because the cells chose not to dysregulate DRD2.

Instead we found that a de novo point mutation in the DRD5 gene, the opposing family member to DRD2, comes up in these cells. So we

took that idea with DRD5 -- next slide -- and looked at the predictive value of this. And it turns out in this particular case, for DR5 the expression, cells that have low DRD6 expression are the ones that are more addicted to DRD2 signaling and respond more strongly to our drug.

So even though the mechanism by which DRD5 is dysregulated is different in innate versus acquired resistance, we still see a common bad actor coming up there. So we started to model this in the lab, but we're looking forward to extending these sort of studies into high-grade gliomas as well.

Next slide. We've also, in addition to the mechanistic studies, performed somewhat of an unbiased screen where you can make cells resistant to the drug, and then just screen for FDA-approved oncology drugs that are already out there to see if we could combine with something to perhaps combat this resistance.

So we're still working to understand the mechanism and the utility of this in high-grade

gliomas, but we have identified combinatorial therapeutics that actually synergize with ONC201 in the acquired resistance setting, and there's an example shown there for cytarabine.

DR. SMITH: Malcolm Smith. I want to drill down just a minute on the mechanism of action. I don't think this has an immediate impact on your clinical plans for the H3 K27M, but in your written report, you describe the potential mechanism of action with mitochondrial protease P. And there are a couple of papers that have described that as a mechanism of action, activating that protease. Cells that expressed the protease were sensitive, and cells that knocked it down were not responsive to the imipridones like ONC201.

I wonder in your hands, what is your experience with the role of mitochondrial protease P, caseinolytic protease P, in the activity of this, of ONC201.

DR. ALLEN: Thank you. You're correct. There are some recent reports in the scientific literature uncovering an additional binding target

of ONC201 called CLPP. This is a recent discovery. It's also a recently posed target for oncology. It's not very well understood in many diseases. It first was uncovered for its role in oncology in the context of the AML.

So the field is still very much figuring out how important this target is for many diseases, including gliomas. What we can say, based on the published evidence, is it's clear that ONC201 does indeed stick to CLPP in addition to DRD2. It's clear from the two published papers in AML and breast cancer that that target can play a role in the activity of the agent.

It's not solely responsible for that when you look at the data, but in fact, when you think about what we're going to do with this information and how we integrate it -- we do have a slide on how we think of the integration of the signaling in particular. Even though there are a lot more studies to be done, we find it interesting that some of the biology actually overlaps with pathways controlled by DRD2. So both CLPP agonist, which

ONC201 does, in addition to DRD2 antagonism, activate the integrated stress response.

It remains to be seen, the utility of this target and its role in gliomas, but we certainly look forward to studying it more, integrating it into this understanding and using it as an additional biomarker in our clinical programs.

DR. SMITH: I think it will be really important to some of the questions earlier if we're looking at DRD2 as the target. In DIPG, maybe that is, and maybe the CLPP clip is very important. I think it will just be really important to play this out and identify what the more important factors related to activity are.

My one comment would be you showed some survival curves and PFS curves, where you basically gave 6 months without events occurring. I'd caution against presenting those kind of figures. There are events that occur in the first 6 months from diagnosis in DIPG, whether they're progression events or survival events.

I think studies like the NRG study that you

described give a good clear answer of what the benefit of ONC201 one is for the DIPG population, but I think allowing 6 months without events will give a misperception of the activity of the agent.

DR. OSTER: Thank you very much for that comment. I appreciate that.

The other comment, which I wanted to make, is that the paper on CLPP has come out just a few weeks before another one comes out in Nature Communications, and that clarifies the binding target DRD2 in much more detail.

DR. BENDER: Two questions relating to preclinical data. I wonder if you have any data about whether ONC201 has either synergistic or additive activity with radiation, which is the current standard of care.

DR. OSTER: Yes, we do have a lot. Actually, we have a few slides on this. Josh? Or is it Sabine? Just to bridge the gap here a little bit, it's obviously a drug which is ideally suited. It's once weekly. It has a very short half-life. Drug-drug interaction risk is through this feature,

relatively minimal, but we have more information.

Sabine, please?

DR. MUELLER: Thank you for that question. That's obviously one of the first we always look at in this disease, looking at radiation. We looked at it in vitro, and you see one cell line that we tested, and we have data on other cell lines very similar, where a CI less than 1 is basically synergy.

I think we obviously see more synergy than in the tumor models, and I think that is obviously one of the reasons why we're also planning to combine ONC201 with this radiation therapy in the clinical trials. What the exact mechanism is and how they synergize, I think it's still something we are looking at and we'll be evaluating. So that's still up for discussion.

DR. OSTER: Does that answer the question?

DR. BENDER: Just a follow-up question. I see the top graph shows, centered, that it might be mediated by T cells. How does the interplay with steroid come into play

DR. MUELLER: I think that that's another great question and a great challenge for our field in general As you know, a lot of these children do require steroids, and I think exactly that interaction. So in one of the planned trials, we are actually specifically looking at this within the biopsy itself.

So I think that's unfortunately something we are still exploring. It's still a topic of research, but it's a great question, and obviously always a great concern of ours, how that interacts with steroids because many of these children do require steroids, especially in the beginning during radiation.

DR. REAMAN: Can you just clarify, while you're there, the preclinical model for the synergy with radiation.

DR. MUELLER: So SF8628 was the cell line that was developed out of an upfront biopsy of a child with DIPG that contains the classic histone mutation, and we have now replicated this with other patient-derived cell lines.

DR. REAMAN: Okay. Thanks.

I also have another question. In the resistance and synergy studies that you presented earlier, did I understand that these were non-glioma models that you tested this?

DR. ALLEN: That's correct. It's a range of solid tumors, but there's been no acquired resistance studies in high-grade gliomas published yet.

DR. REAMAN: Then in those solid tumors, was there evidence of efficacy, and exactly what solid tumors, and what led you to develop exclusively in midline gliomas?

DR. ALLEN: In terms of the mechanism of resistance, we certainly looked at these sort of studies in a range of settings, and find that the mechanisms of resistance can vary. So what I mean is in a tumor type that's very sensitive to ONC201, the way they evolve resistance can be different from ones that are only marginally sensitive.

We see a consistent dysregulation of the DRD5 pathway, but I think, like I mentioned before,

how the cells choose to dysregulate that pathway can vary. It can be through expression mechanisms, it can be through epigenetics, or it can be through gain of function mutations. That's generally the spread that we see.

For the second part of your question, the specific emphasis on H3 K27M mutant glioma and the clinical development of this agent really sprung from the anecdote that Dr. Wen presented in his presentation. It was really a serendipitous finding.

At the time we discovered this drug and initially profiled it in preclinical studies, the H3 K27M mutation had not been found at that time. So it was really a serendipitous finding in this one outlier response that took us back to the lab, and we wanted to understand why that patient responded so well and take that forward.

DR. OSTER: If I can just add to that just one comment. Our whole early clinical development program was designed to find efficacy with a single agent. Actually, when you look at the profile of

the drug, we have efficacy in a multitude of models, but we believe that in this particular clinical indication, H3 K27M, this represents an area where we can actually have enough efficacy to get the drug approved.

We are working a lot on synergistic rationales in other tumors. For example, we have significant biological activity in endometrial cancer, and we want to combine it there with taxol. We have other models where we actually think about using combinatorial approaches.

DR. LUDWINSKI: Donna Ludwinski. I was wondering if you could comment -- back to Dr. DuBois question about neuroblastoma -- on an investigator initiated trial for NERC endocrine tumors that neuroblastoma is eligible for? It is an adult phase 2. I'm not sure if you can comment on that, if any neuroblastoma --

DR. OSTER: Sure. It's at the Cleveland Clinic.

DR. LUDWINSKI: Yes.

DR. OSTER: We can comment on this. It's a

mix of different diagnosis that we are exploring to find if these neuroendocrine tumors actually respond. We have some interesting observations.

DR. ALLEN: Yes, absolutely. And it really fell out of the same kind of rationale that was presented earlier. Even without doing a lot of preclinical work, you can automatically think of a lot of tumors where dopamine might be dysregulated. So to that end, yes, a phase 2 investigator initiated trial predominantly focused on adults, because at that time we didn't have pediatric safety data.

It was initiated. There are multiple arms to the study. There was a lot of emphasis initially on pheochromocytoma and paraganglioma because when you rank order, the amount of expression of different components there, it really sticks its head out. There we've had interesting anecdotes and signs of regressions in a few patients, but the trial is not formally read out yet. It's still very early.

DR. PAPPO: One final question, Julia?

DR. BENDER: So I'm asking this question actually as an optimist and not as a pessimist. I want to be clear because I recognize what the prognosis is for DIPG. But I'm wondering if there is any preclinical juvenile tox data to let us anticipate
what might be a long-term toxicity in a young patient.

DR. STOGNIEW: Martin Stogniew. We take it as a positive question.

(Laughter.)

DR. STOGNIEW: The short answer is we've not done any juvenile toxicity study in animals, and in fact the FDA has published papers on that they generally are not very predictive of adult data. Currently, we plan to do two more additional rat and dog studies, but unless we see a specific signal, we currently don't plan to do juvenile toxicity data.

DR. OSTER: Yazmin, please? Dr. Odia from Miami Cancer Institute.

DR. ODIA: Yazmin Odia, Miami Cancer

Institute. I would add to that that the first pediatric experience, which has now been published, was a 10-year old young lady who received a treatment for over 2 years without any negative toxicity, and only discontinued treatment because of progression.

DR. OSTER: Thank you.

Open Public Hearing

DR. PAPPO: Thank you very much. We will now proceed to the open public hearing session.

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

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

Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

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

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

Will speaker number 1 step up to the podium

and introduce yourself? Please state your name and organization you're representing for the record.

DR. MUSELLA: Hi. First I'll go to the disclosure in the middle of my speech. My name is Al Musella. I'm the president and founder of the Musella Foundation for Brain Tumor Research and Information, Incorporated a 501(c)(3) nonprofit public charity, dedicated to helping families that are dealing with brain tumors.

I am also a member of the DIPG Collaborative, the DIPG All-In Initiative, and I'm a member of the Society of Neuro-Oncology's clinical trials working group. I've been doing this for 25 years, and I got started because two family members were battling glioblastomas.

My biggest fear was always that the cure was available someplace in the world, and we either didn't know about it or couldn't get access to it, so I started my organization to identify all available treatments and help get access to them.

When the results of the ONC201 and DIPG and diffuse midline glioma were presented to the

public, my members were clamoring to get access to it, but most weren't able to get it. So I approached the company and asked if they could reopen the ONC201 compassionate use program, which they previously closed. They refused saying they did not have the resources to handle a program anymore, as they were being inundated with compassionate use requests and had to concentrate the effort on the clinical trials.

I offered to pay for the program and help run it in such a way that we might be able to use the results from it to help support FDA approval. I formed a collaboration with Cancer Commons and xCures, and we launched the Xcelcia study, which is on clinicaltrials.gov, which was designed to collect real-world evidence on cancer treatments outside of the clinical trial system, using approved drugs, or off-label drugs, or compassionate-use treatments and combinations of treatments, and learning from every single patient.

Oncoceutics accepted my proposal, and I formed another collaboration with the Michael

Mosier Defeat DIPG Foundation and The Cure Starts Now to pay for the compassionate use program in the USA. As to the disclosure, this was set up as venture philanthropy, where my organization and xCures will get a return if the drug becomes a success. We have never received anything from the company so far.

We started the compassionate use program, and it is in high demand. We enrolled over 40 patients already in just the first few months, which shows the fantastic need for this drug. Requests are increasing as more data like that presented today becomes available. We are tracking these patients to look for side effects as well as efficacy. Although it's too early to report on, a few of the patients had remarkable responses, something I've never seen in my 25 years experience with these tumors.

There are still many patients who want access to this treatment, and we cannot help them, as they do not qualify for the clinical trial or for the compassionate use program, or they simply

live too far away from a participating center. The most heartbreaking thing in the world is when a mother calls me and tells me about their child, and asks for access to this drug, and I have to say no. This keeps me up at night, as I think of my own kids and how I would feel in the situation. This happens a few times a week.

I want to request that the FDA consider approving this drug immediately. Over 350 patients have used the drug with little serious side effects. There are some cases of amazing responses involving improvements in walking, cranial nerve palsy, children being able to remain in school while on treatment, and living longer than expected and in good shape, and this is something we just haven't seen before.

I understand we really need much more data. However, I believe we can get definitive proof of efficacy and safety after the approval by requiring all the patients who take the drug to be followed in a registry. The FDA can then evaluate the results continuously to confirm the risks and

benefits of the drug. This would allow patients to get quick access to the drug, and the risk of not getting the drug at this point is way higher than the risk of possible side effects.

There are few precedents where the FDA granted approval based on much smaller number of patients for other serious rare diseases. If you don't feel there's enough survival data for full approval, then consider accelerated approval based on improvements in the neurological functions, the ability to go to school for longer periods of time, and these things are providing meaningful benefits right now to patients over the existing therapies.

My organization has a program where teams of experts, including a large virtual tumor board, evaluate patients and offer ideas for treatments, and then we follow a patient to see how it works. Invariably, these patients with the H3 K27M mutation have ONC201 at the top of the list of options. There really is nothing else available with the same risk-benefit ratio. We need this approved so they can get it easily and quickly.

Following all patients on ONC201 in the real world after approval will let us quickly learn the best ways to use it, which combinations might work the best, and finally give some hope to these patients who never had any hope before. Thank you.

DR. PAPPO: Thank you very much. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. HOOGENDOORN: My name is Ami Hoogendoorn. I do not represent any organization, and I have not received anything financial to be here. I'm here today to represent this little girl, my daughter, Emerson. In the spring of last year, Emerson began experiencing terrible headaches and backaches, as well as extreme fatigue, dizziness, and double vision.

We could tell something was wrong. Our girl, who normally we had to beg to sit still or go to sleep, was not able to keep her eyes open on a short car ride. She didn't want to take part in activities she once loved like T-ball or playing

outside, and she was constantly uncomfortable, waking up at all hours of the night in pain.

Finally, just days after graduating kindergarten, we took Emerson to the emergency room where she had an MRI. They found a mass in her brain, and she was ambulanced to the nearest children's hospital. She stayed in the hospital for 11 days, where she underwent two large and invasive brain surgeries.

We soon learned from biopsies that Emerson had a cancer known as diffuse midline glioma. When the doctors told us our sweet rainbow baby had a rare and aggressive form of brain cancer, we were devastated, and our hearts were broken. Emerson underwent the standard form of treatment for this cancer, which was daily radiation and oral chemo for 6 weeks. When that was wrapping up, we wanted to know what the next step was to rid our girl of her cancer. Giving up was not an option, and being hopeless was not an option.

We knew of a pediatric clinical trial of ONC201 at another children's hospital not too far

away, which Emerson luckily qualified for. Our doctor reached out to enroll her only to find out there were no spots available. We intended to apply for compassion care, hoping for an opening, and after returning from Emerson's make a wish trip, we hoped to continue on other medications to keep her tumor at bay as long as possible. The next day we received a call from Emerson's doctor telling us there had been an opening for the trial at the University of Michigan, and it was Emerson's. She began the trial this past September just after Labor Day.

It is very likely that Emerson would not be here today if it weren't for ONC201. At the beginning of the trial, her tumor was irritated and increased to 125 percent in size following radiation. However, at the last scan, which was just in the middle of May, her tumor is now only at 23 percent of its original size. I believe her photos were the 6 year old that you saw in the presentation.

As you can see her here, you can't tell that

she has cancer from looking at her. Her main complaint from ONC201 is that she can't eat for the 4 hours, and she's often tired after staying up late because she wants to snack before going to bed after taking her medicine.

Many children with cancer have to stay in the hospital for days or weeks to receive treatments. ONC201 allows Emerson to live a fully normal life outside of the hospital. Many cancer patients have a port, which is uncomfortable and gets in the way of bathing and swimming, but ONC201 allows Emerson to swallow 3 pills a week and swim in her grandma's pool any time she wants.

Emerson has not needed any hospitalizations, any medical intervention. She hasn't vomited or lost all her appetite like many cancer patients do. Emerson's Energy has returned. Her passion for school and playing outside his back. Her goofy, silly side is back. Emerson is able to be herself again with no side effects from the medication. She's able to be and do anything every 7-year-old girl wants to do.

Emerson graduated from first grade a few weeks ago, where she was at or above grade level all year. She even felt great enough to participate in gym and play at recess. Emerson began taking piano lessons, which she loves. She's able to spend all day swimming at grandma's pool and jumping on the trampoline.

Emerson missed tennis this morning and a softball game last night so that we could be at this meeting. Her summer schedule is packed full of the activities every child deserves to have the opportunity to participate in. Emerson's future looks bright and hopeful and possible because of ONC201 and what it has done to her tumor. Why not allow other patients the same hope and possibility with a medication that has little consequence? Thank you.

(Applause.)

DR. PAPPO: Thank you very much.

Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the

record.

MS. BARTEE: My name is Anjalie Bartee. I was on, and am still on the ONC201 trial. July 20, 2018, I got diagnosed officially with DIPG. I went through 6 weeks of chemo and radiation, and then after the chemo and radiation, we did an MRI, and my tumor had grown, and it grew down more to my brain stem -- well, to the top of my brain stem.

Dr. Schwartz in Omaha, Nebraska, referred us to Dr. Koschmann in Michigan to take the drug, and he said that the side effects wouldn't be nearly as aggressive as the side effects with chemo, which I had horrible side effects because it targeted the dopamine receptors in the tumor.

We started ONC201 officially on October 24, 2018. The side effects that I had from it were basically nothing, except for like over-salivating, which is an easy price to pay when before I was puking all the time, and now I can live longer; so a little over-salivation isn't too bad.

After my MRI from being on ONC201, the tumor shrunk. After growing from chemo and radiation, it

shrunk to over 50 percent. On the stack of papers that you guys got, on slide 30, mine is on the right side of the 17 year old.

My two goals, once I was diagnosed and given a really short prognosis, was to graduate high school and to reach my birthday. I graduated high school in May, and my birthday is actually today, so I reached both of those goals. The community of people with DIPG is so strongly connected. We all grieve together when someone passes away, so it would be really nice if we could all heal together and get well together by making this drug accessible.

My family lives in Nebraska, so the traveling was -- it's 10 hours to Michigan, and in the beginning, it was every 3 weeks, and then later on, the FDA approved that we would be able to come every 9 weeks. And being a 17 year old at the time with cancer, it was very strenuous doing 10 hours of travel every 3 weeks to Michigan. But it was well worth it because my tumor has shrunk so much when I didn't even think that I would be alive now,

let alone however longer I have to be alive. Even my doctor in Nebraska said that the trial was throwing her off because she thought that I would be way worse 7 months after when most people die.

Next month, on the 20th will be a year since diagnosis, and I'm really happy because, obviously, a lot of people don't get that.

(Applause.)

DR. PAPPO: Happy Birthday. Thank you.

Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. MOSIER: Good afternoon. My name is Jenny Mosier. I'm here today as a parent whose child died from diffuse intrinsic pontine glioma and as the executive director of Michael Mosier Defeat DIPG Foundation, a nonprofit that funds medical research to find a cure for DIPG. Our foundation has made grants to support development of ONC201 as a potential therapy for DIPG patients but has no financial interest in ONC201 or

Oncoceutics. I appreciate the opportunity to speak today.

As a parent and a DIPG advocate, I would like to highlight three important points for the subcommittee's consideration. First, development of ONC201 should include the population of children fighting DIPG. There is an urgent need for therapies for DIPG as illustrated by the story of my own son, Michael.

On September 4, 2014, one week after Michael's 6th birthday and the start of kindergarten, we learned he had a brain stem tumor. In shock, we were told that surgery was not an option and that he probably would not live to see his 7th birthday. We quickly learned that DIPG had no viable treatments and near 0 percent survival. Tragically, DIPG does not only lead to the death of way too many children, it also inflicts substantial suffering on many of these kids as they fight the disease.

Around 6 weeks after my son's diagnosis, he was unable to walk on his own. The tumor paralyzed

Michael's body over a period of months. It gave him double vision. It made him constantly nauseated, so he would often vomit and could only sleep if elevated. The tumor stole his ability to smile. It stole his voice. It made it difficult to chew and swallow. It eliminated his bladder control. The steroids he took doubled his weight over a period of months.

At the end of Michael's life, he could not move any part of his body or speak. The last thing he could do was blink and respond to yes/no questions, and then that went away, too. Michael fought for 8 and a half months, and he suffered tremendously. He did not make it to his 7th birthday.

It is essential that decisions surrounding ONC201 as a potential treatment for this vulnerable patient population are viewed through a lens that takes account of the terminal nature of DIPG, as well as the toll it takes on children during their fight. Second, FDA should utilize all tools available to expedite development and approval of

ONC201 for DIPG.

The median survival from diagnosis for a child diagnosed with DIPG is only 9 months. DIPG epitomizes a serious condition with unmet medical need. Children who are fighting DIPG right now cannot afford delay and desperately need options. Any steps that advance approval by months could give these kids access to a treatment that has the potential to extend their survival.

There is also a need for therapies for DIPG with a better side effect profile. Our son took an experimental drug coupled with an FDA-approved chemotherapy that was given 1 week per month. I was supposed to wear gloves just to handle the medication. For a few weeks after he took the drugs, Michael took anti-nausea medicine around the clock.

If we missed a dose, Michael would typically vomit right away. For a few weeks, Michael would be very tired, hardly speak, and lose interest in activities in school. He would have around a week when his energy would rebound, and then it was time

to do it all over again.

While further study is needed, ONC201 shows promise to offer improved tolerability to DIPG patients. I have spoken with a number of parents whose children have taken ONC201 through the clinical trial or compassionate use. I have also interacted personally with the children while they are on a treatment protocol. Families have shared that their children need some anti-nausea medicine on the day they are taking the drug, but that they typically feel better within a day or two and can quickly resume normal activities. We urge FDA to use all tools at its disposal to expedite development and approval of ONC201 for DIPG.

Third, while ONC201 continues to be studied through clinical trials, FDA should take steps within the trial context or through expanded access to enable as many patients as possible to gain access to the drug. My role allows me to regularly interact with DIPG families, and many are frustrated because they've been unable to access ONC201 or other treatments for their kids.

When a child is facing a terminal disease, we should be eliminating impediments that block access to experimental treatments, especially when they offer potential benefit with limited side effects. We need progress for children with DIPG. These kids deserve a chance for a future. Thank you to the FDA and to the subcommittee for allowing me to speak today.

(Applause.)

Questions to the Subcommittee and Discussion

DR. PAPPO: Thank you very much.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The subcommittee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

We will now proceed with the charge and questions to the subcommittee and panel discussions. I would like to remind the 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 question number 1.

Dr. Reaman, would you like to read it or would you like for me to read it?

DR. SINGH: Sonia Singh. The first question we'd like to pose to the committee is, given the mechanism of action of ONC201 and broad antitumor activity observed in a range of preclinical cancer models, please discuss possible options for evaluation of ONC201 in pediatric preclinical tumor models and possible pediatric development of ONC201 beyond high-grade gliomas.

DR. DuBOIS: I think we've addressed this somewhat already in the Q and A with the sponsor. It's, I think in my view, terrific that the agent's being evaluated through the PPTC mechanism. That shouldn't in any way delay development where there's already a signal in H3 K27M glioma.

DR. PAPPO: I agree. I was wondering if also just briefly looking at our RNA-seq data and just trying to identify potential signals in a variety of different pediatric tumors or many, many

clouds [ph] that could allow you to look at large numbers of pediatric tumors and tried to identify potential tumors that could be tested a little bit more efficaciously and expeditiously in the PPTP.

DR. REAMAN: Just a point of clarification that we're really not here to discuss potential approval in a specific indication. Our reason for being here today is to ascertain your interest in evaluating this drug through the written request mechanism.

The written request mechanism, from the Best Pharmaceuticals for Children Act, requires evaluation of an investigational drug in any and all possible pediatric indications, where there may be a potential benefit or public health. So that's the reason for this question, and I think we should confine our discussion really to whether or not a written request might be a consideration at this point, and the issue of approval or non-approval in DIPG or any other indication is really outside the purview of this discussion.

DR. PAPPO: Thank you for the clarification.

Malcolm?

DR. SMITH: Greg, just to clarify, there's a program for DIPG in the K27M patient population. That seems appropriate and presumably could be the focus of a written request, correct?

DR. REAMAN: It could be the focus, but as I mentioned, the legislation requires evaluation in any other. So our question is what other potential indications might there be? And I don't know that we have a real answer to that question.

DR. SMITH: Right. And I think it gets to the question that I was asking and the importance of understanding a DRD2-based mechanism of action versus something that may involve CLPP more. At this point, we really don't have experience with either mechanism of action in terms of knowing which pediatric cancers are relevant to those mechanisms of action.

I think in vitro screening that the PPTC is doing, other screening like that, could help provide signals. But I do think it will be useful for researchers studying the ONC201 and related

compounds to really kind of nail down when one mechanism or the other is more important for the anticancer activity.

DR. PAPPO: To briefly summarize the discussion on this specific question, there is definitely interest in trying to identify other potential pediatric cancers that could benefit from this drug. It is important also to clarify which is the primary mechanism of action of this drug, whether it's through DRD2 or CLPP, and to identify which are the pediatric cancers that are relevant to either of those two targets and to better clarify their mechanism of actions on how to better identify those cancers that could benefit from this drug.

Does that summarize it? Malcolm, anything else? Thank you.

We will now proceed with question number 2.

DR. SINGH: Please discuss the CNS penetration properties of ONC201 and any potential role in addressing brain metastases in children.

DR. PAPPO: If there are no questions or

comments concerning the wording or the question, we will now open the question for discussion.

DR. BENDER: I would just say in response to this question that many times, CNS metastasis is an exclusion criteria in phase 2 trials. I think that the data that we have seen in high-grade glioma would mean that this would be a drug for which when we do broad phase 2 studies, we would want to be very clear, actually, that CNS metastases are included, and perhaps even have a designated strata to study them.

DR. PAPPO: Comments regarding the PK and the PD? Go ahead, Greg.

DR. REAMAN: Just a comment that there has been a recent FDA guidance on re-evaluation of eligibility criteria. We are certainly in agreement that perhaps for good reason or not so good reasons, patients with CNS metastases have traditionally been excluded, but we agree that in appropriate situations, that should be re-evaluated and reconsidered.

DR. PAPPO: Any other comments or any

questions?

(No response.)

DR. PAPPO: If I can summarize this brief discussion for question number 2, given the good CNS penetration and the activity in certain tumors of ONC201m we believe that patients that have brain metastases that are eligible for a trial should not be excluded for trial participation.

We will now move on to question number 3.

DR. SINGH: Please consider the plans for administering ONC201 in combination with other treatments such as radiation therapy, targeted therapies, or chemotherapy regimens, and recommendations for isolating the effect of ONC201.

DR. PAPPO: If there are no questions or comments concerning the wording or the question, we will now open the question for discussion. I believe that that was briefly touched upon when they were doing the presentation on the additive effect that it has with the radiation therapy. I don't know if anybody else wants to weigh in a little bit more or have any other concerns or

comments.

Steve?

DR. DuBOIS: I suspect that this question is getting more at the design of a trial that would demonstrate definitive evidence of activity in a disease where radiotherapy is the standard. My own view is given the very robust historical data in frontline DIPG, that the a comparator arm in this case would not be needed. I think one could rely on that very robust historical control to isolate the effect of ONC201.

DR. PAPPO: Agreed. Any other comments?

(No response.)

DR. PAPPO: Just to add on to the discussion, we will also say that given the very strong data on historical controls, we can use that as a comparator arm in a prospective study of ONC201.

We will now move to question number 4.

DR. SINGH: Please address any potential short-term or long-term toxicity unique to the pediatric population that might justify exclusion

of any pediatric age groups not planned for study; For example, patients younger than 2 years of age are ineligible in ongoing study ONC014.

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

DR. BENDER: I think that we did not get the opportunity when Oncoceutics was speaking about formulation, but I would curious to know if this is part of the issue. Otherwise, again, given this diagnosis, particularly for this disease, I don't see a good reason to exclude the younger patient.

DR. SMITH: And I don't think we have evidence for particular toxicities in the younger patients. I think just in terms of clinical trial design, because the children less than 3 years of age may have a different prognosis than children older than 3 years of age, even if the younger children are enrolled on the trial, the historical control would best be made to the older children in terms of ascertaining the efficacy of ONC201 in the newly diagnosed DIPG population.

DR. DuBOIS: Just to pick up on Julia's point about the formulation, I think that's also important in a DIPG context, where those patients, even if they're traditionally old enough to swallow pills, often have swallowing dysfunction as a result of the tumor itself. So I think thinking about a non-pill formulation is really going to be important.

DR. PAPPO: Any other comments pertaining to this question? Ted?

DR. LAETSCH: I would just agree with what the other speakers have said. The comment around the different prognosis of younger patients is important, but I would also argue that it's important to define the dose for these young patients. Even if the efficacy comparison is made in the older patients, to do that study and then potentially extrapolate efficacy to younger patients would be important.

DR. PAPPO: Any other comments or questions?

(No response.)

DR. PAPPO: So to briefly summarize the

discussion for question number 4, an issue was brought up to pay attention to the formulation and better define a dose for this younger population; that the age of those younger patients, especially less than 2 years of age, should not be an exclusion criteria for clinical trial participation. At least based on the data that has been presented, there does not appear to be evidence for a specific or particular toxicity in using this drug in the population that has been tested.

I wanted to add just a very minor thing. It's probably irrelevant, but it just caught my eye. About 10 to 12 percent of patients that were taking the drug fell, so I don't know if that's something that just needs to be kept in mind. For very young patients are already starting to walk and are already unsteady; if there has to be some particular attention to that group of patients, maybe wearing a helmet or something because you don't want them to --

We will now proceed with question number 5.

DR. SINGH: Please comment on the potential endpoints that could be used in future clinical trials designed to evaluate the isolated efficacy of ONC201 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.

DR. SMITH: Well, I think I'll just -- Steve made the point earlier that for DIPG, we have a very robust historical control experience within COG, within the PBTC, and others, and overall survival is the typical endpoint used for those studies. So I think a trial enrolling patients newly diagnosed and receive radiation and ONC201 with an overall survival endpoint will ascertain whether the agent truly has benefit for this population.

I think for the other, for neuroblastoma, and for other tumors, I think what the company did, looking for signals of activities, single agents, signal activities, really has a lot of merit. That's why we're talking about K27M today, is

because they identified activity.

So if preclinical signals are identified and there are clinical trials for other pediatric patients looking for that single agent, seeing the signal will help guide development. Then once you have a signal, you can decide what kind of studies you'd need to do to truly document benefit. But having that signal will be really important.

DR. BENDER: I agree that having a signal is very important as a single agent, but also wonder if consideration could be given to allowing patients to, after having a signal, actually receive radiation in addition while on the study for those other diseases; given the data that we'll have about the combination and the fact that oftentimes a patient on a clinical trial would also benefit from radiation, and you have to choose between radiating or entering on the clinical trial.

So if there were a window of opportunity to test the drug but then that it could also receive radiation, that might be a nice trial design.

DR. PAPPO: Other questions, or concerns, or comments?

(No response.)

DR. PAPPO: To briefly summarize the comments for question number 5, as far as clinical trial design for newly diagnosed patients with DIPG, we all agree that we could use a historical control for the comparator, and overall survival would probably be the gold standard for an endpoint. As far as for other diseases, once a signal is identified, then we could decide what would be the best way to proceed as far as defining an endpoint for identifying activity of ONC201.

Also, it was brought up the possibility that for other diseases, since there appears to be evidence that combination with radiotherapy and ONC201 might be synergistic, to allow the opportunity for some of those patients to have local therapies after they've received a few cycles of this drug alone.

Did I summarize that correctly? Any other comments or anything I missed?

(No response.)

Dr. Reaman will now provide closing comment.

FDA Closing Remarks - Gregory Reaman

DR. REAMAN: Well, I'd first like to thank the sponsor for coming and presenting the information, background data, and the clinical data to date on ONC201. Obviously, I thank all of the advisors. It's not surprising that we all firmly recognize and believe that there is a huge unmet need for new therapies in the disease that you have evaluated ONC201 in to date, and we certainly applaud that.

I think the discussion that we've had is beneficial, and the testimony that we've heard from patients and families has been extraordinary, so thank you all for this participation.

Adjournment

DR. PAPPO: Thank you, Greg.

We kindly ask that all attendees dispose of any trash or recycling in the proper receptacles in the hallway and not leave any waste items on the floor or tables. Panel members, please remember to

take all personal belongings with you, as the room is cleared at the end of the meeting today. Please leave your name badge on the table so that it may be recycled. All other meeting materials left on the table will be disposed of.

We will now adjourn the meeting. Thank you very much, and we'll see you again next year.

(Whereupon, at 2:28 p.m., the afternoon session was adjourned.)