



**Final Summary Minutes of the Pediatric Subcommittee of the  
Oncologic Drugs Advisory Committee Meeting  
June 20, 2019**

The Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on June 20, 2019, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided the briefing materials from the FDA and Oncoceutics, Inc. The meeting was called to order by Alberto S. Pappo, MD (Chairperson). The conflict of interest statement was read into the record by Lauren Tesh Hotaki, PharmD, BCPS (Designated Federal Officer). There were approximately 55 people in attendance during the morning session and approximately 80 people in attendance during the afternoon session. There were no Open Public Hearing (OPH) speaker presentations during the morning session and four (4) OPH speaker presentations during the afternoon session.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

**Agenda:** During the morning session, the particular matter for this meeting was reviewed and discussion of the FDA Reauthorization Act of 2017 (FDARA) mandated Relevant Pediatric Molecular Target List posted on the FDA website: <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm>. FDA is required by statute to review and update the previously approved and published lists. The focus of the discussion was limited to two target “classes” included in the Relevant Pediatric Molecular Target List: (1) targets linked to cell lineage and (2) targets on normal immune cells and cells in the tumor microenvironment. Planned introductory presentations were on: (1) cell-based therapy approaches to childhood cancer and (2) novel membrane antigen determinants in pediatric tumors.

During the afternoon session, information was presented to gauge investigator interest in exploring potential pediatric development plans for a product in development for adult cancer indications. The subcommittee considered and discussed 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 also provided information to the Agency pertinent to the formulation of written requests for pediatric studies, if appropriate. The product under consideration was ONC201, presentation by Oncoceutics Inc.

**Attendance:**

**ODAC Members Present (Voting):** Alberto S. Pappo, MD (pedsODAC Chairperson); Courtney J. Preusse, MA (Consumer Representative); Brian I. Rini, MD, FACP

**ODAC Members Not Present (Voting):** Massimo Cristofanilli, MD, FACP; Susan Halabi, PhD; Cristian S. Hinrichs, MD; Philip C. Hoffman, MD; Heidi D. Klepin, MD, MS; Grzegorz S.

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Nowakowski, MD; Vassiliki A. Papadimitrakopoulou, MD; Gregory J. Riely, MD, PhD; Alice T. Shaw, MD, PhD; Thomas S. Uldrick, MD, MS

**ODAC Member Present (Non-Voting):** Phuong Khanh (P.K.) Morrow, MD, FACP (Industry Representative)

**Temporary Members (Voting):** Anne L. Angiolillo, MD; Catherine Bollard, MBChB, MD (Morning Session Only); Steven G. DuBois, MD; Ira J. Dunkel, MD (Morning Session Only); Julia Glade Bender, MD; Naynesh R. Kamani, MD; Theodore W. Laetsch, MD; Donna M. Ludwinski (Patient Representative); Nirali N. Shah, MD, MHSc; Malcolm A. Smith, MD, PhD

**FDA Participants (Non-Voting):** Gregory Reaman, MD; Sonia Singh, MD; Nicole Drezner, MD; Sandra Casak, MD

**Designated Federal Officer (Non-Voting):** Lauren Tesh Hotaki, PharmD, BCPS

**Open Public Hearing Speakers:** Morning Session: None; Afternoon Session: Al Musella, DPM (Musella Foundation For Brain Tumor Research & Information, Inc.); Ami Hoogendoorn; Anjalie Barte; Jenny R. Mosier (Michael Mosier Defeat DIPG Foundation)

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*The morning session agenda was as follows:*

Call to Order and Introduction of Subcommittee

**Alberto S. Pappo, MD**  
Chairperson, pedsODAC

Conflict of Interest Statement

**Lauren Tesh Hotaki, PharmD, BCPS**  
Designated Federal Officer, ODAC

Introductory Remarks:  
Relevant Molecular Targets for Cancer  
Drug Development for Children

**Gregory H. Reaman, MD**  
Associate Director for Pediatric Oncology  
Oncology Center of Excellence  
Office of the Commissioner  
Associate Director for Oncology Sciences  
Office of Hematology and Oncology Products  
Office of New Drugs, CDER, FDA

**GUEST SPEAKER PRESENTATION**

Immunotherapies for Pediatric Cancer:  
Current Status and Future Prospects (with  
an emphasis on Targets)

**Crystal L. Mackall, MD**  
Ernest and Amelia Gallo Family Professor of  
Pediatrics and Medicine  
Director, Stanford Center for Cancer Cell  
Therapy  
Director, Parker Institute for Cancer  
Immunotherapy at Stanford  
Associate Director, Stanford Cancer Institute

Stanford University

Clarifying Questions

**GUEST SPEAKER PRESENTATION**

Immunogenomic Approaches to More  
Effective Childhood Cancer Therapies

**Kris Bosse, MD**  
Assistant Professor of Pediatrics  
Perelman School of Medicine at the  
University of Pennsylvania  
Evan Lindberg Neuroblastoma Research  
Scholar  
Attending Physician, Division of Oncology  
Children's Hospital of Philadelphia

Clarifying Questions

**BREAK**

**OPEN PUBLIC HEARING**

Questions to the Subcommittee and  
Subcommittee Discussion

**LUNCH**

*The afternoon session agenda was as follows:*

Call to Order and Introduction of  
Subcommittee

**Alberto S. Pappo, MD**  
Chairperson, pedsODAC

Conflict of Interest Statement

**Lauren Tesh Hotaki, Pharm.D, BCPS**  
Designated Federal Officer, ODAC

Introductory Remarks

**Gregory H. Reaman, MD**

**INDUSTRY PRESENTATION - ONC201**

**Oncoceutics Inc.**

ONC201: The First Imipridone for the  
Treatment of H3 K27M-mutant High Grade  
Glioma

**Wolfgang Oster, MD, PhD**  
Chief Executive Officer, Oncoceutics Inc.

**Josh Allen, PhD**  
Senior Vice President of R&D, Oncoceutics  
Inc.

**Patrick Wen, MD**  
Professor, Neurology, Harvard Medical School  
Director, Center For Neuro-Oncology

Dana-Farber Cancer Institute

**Sabine Mueller, MD, PhD**  
Assistant Professor of Clinical Neurology  
University of California at San Francisco  
Hellen Diller Family Comprehensive Cancer  
Center

Clarifying Questions

**OPEN PUBLIC HEARING**

Questions to the Subcommittee and  
Subcommittee Discussion

FDA Closing Remarks

**Gregory H. Reaman, MD**

**ADJOURNMENT**

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*Questions to the Committee:*

**Morning Session: Issues Relating to the Development of the Targets Associated with Specific Cell Lineage Determinants List**

1. **DISCUSSION:** Please discuss any new or emerging data that provide sufficient evidence for the addition of a molecular target to the List of Molecular Targets Associated with Specific Cell Lineage Determinants.

*Committee Discussion:* Members of the subcommittee suggested adding several targets to the current list including: Cluster of differentiation (CD) 99, Pregnancy-associated plasma protein-A (PAPP-A), Insulin-like growth factor binding protein-like 1 (IGFBPL1), and Paired-like homeobox 2B (PHOX2B). The subcommittee agreed that sufficient evidence was present for the addition of the four molecular targets mentioned. Please see the transcript for details of the subcommittee's discussion.

2. **DISCUSSION:** Please discuss any new or emerging data that provide sufficient evidence that a relevant target currently on the list should be removed.

*Committee Discussion:* The subcommittee members made no comments on the removal of any relevant target currently on the List of Molecular Targets Associated with Specific Cell Lineage Determinants. Please see the transcript for details of the subcommittee's discussion.

3. **DISCUSSION:** Please discuss any new or emerging data that provide sufficient evidence for the addition of a molecular target to the List of Relevant Targets on Normal Immune Cells and Cells in the Tumor Microenvironment.

***Committee Discussion:** The subcommittee members suggested moving Transforming growth factor beta (TGF $\beta$ ) receptors to this list from the “Others” list and adding Interleukin 15 (IL-15), Hypoxia-inducible factor (HIF), V-domain Ig suppressor of T cell activation (VISTA), Colony-stimulating factor 1 receptor (CSF1R), and CD105 to the target list. One committee member commented on the current usage of several oncologic agents for pediatrics that target IL15 receptors. Both VISTA and CSF1R were mentioned to have active, ongoing trials that provided justification for addition to the list. In addition, a subcommittee member referenced Vascular endothelial growth factor (VEGF) targets being relevant in the adult oncology space and questioned their relevance in the pediatric world. Another member noted data that highlighted CD105 and its compensatory pathway for VEGF inhibition. Please see the transcript for details of the subcommittee’s discussion.*

4. **DISCUSSION:** Please discuss any new or emerging data that provide sufficient evidence for the deletion of a target on this list.

***Committee Discussion:** The subcommittee members made no comments on the removal of any relevant target currently on the List of Relevant Targets on Normal Immune Cells and Cells in the Tumor Microenvironment. Please see the transcript for details of the subcommittee’s discussion.*

5. **DISCUSSION:** Please discuss specific recommendations for how best to evaluate and/or prioritize combinatorial approaches to evaluating agents directed at targets on normal immune cells.

***Committee Discussion:** The subcommittee discussed the need for strong preclinical data or substantial data from adult combination models that provide promising signals before starting combinatorial approaches in the pediatric oncology space. A subcommittee member stated the need for caution when considering combinatorial approaches, given the fact that we do not have a full understanding of the potential toxicities when combining these agents. Another subcommittee member commented that current chimeric antigen receptor T (CAR-T) cell therapy is a combination therapy with lymphocytes. In the discussion of CAR-T therapy, another member mentioned the associated antigen loss observed with CAR-T therapy and the importance of rational decision making on multiantigen targeting strategies to ensure durable remissions. Furthermore, suggested combinations included: (1) checkpoint inhibitors and immune-based therapies, (2) T cell activation, and (3) epigenetic modifiers to enhance T cell function. Another subcommittee member commented on strategies needed to upregulate major histocompatibility complex (MHC) loss were vital which also included comments on using nanotherapy targeted approaches or some small molecule delivery systems. In addition, one member mentioned that adding other therapies, such as chemotherapy, could represent a regulatory challenge on how to determine how effective*

*immune-based therapy was. Please see the transcript for details of the subcommittee's discussion.*

### **Afternoon Session: Issues Relating to the Development of the Targets on Normal Immune Cells and Cells in the Tumor Microenvironment List**

1. **DISCUSSION:** 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 pre-clinical tumor models and possible pediatric development of ONC201 beyond high grade gliomas.

**Committee Discussion:** *The subcommittee agreed that the Pediatric Preclinical Testing Consortium (PPTC) is the right mechanism for evaluating this agent and should be considered for ONC201 in pediatric pre-clinical tumor models and possible pediatric development of ONC201 beyond high grade gliomas. The subcommittee further commented that given the uncertainty in determining when, where, and whether the Dopamine receptor D2 (DRD2) or Caseinolytic mitochondrial matrix peptidase proteolytic subunit (ClpP) mechanism is effective for anticancer activity, further evaluation is needed to clarify and understand the relevance of its true mechanism of action. The subcommittee stated their interest in trying to identify other pediatric cancers and to identify which are the pediatric cancers that are relevant to those two targets (DRD2 and ClpP). Please see the transcript for details of the subcommittee's discussion.*

2. **DISCUSSION:** Please discuss the CNS penetration properties of ONC201 and any potential role in addressing brain metastases in children.

**Committee Discussion:** *The subcommittee agreed that designated strata should be in place to study central nervous system (CNS) metastases. The subcommittee also agreed that broad phase 2 studies should clearly state that CNS metastases are included to be able to understand the CNS penetration properties of ONC201 and its potential role in addressing brain metastases in children. One member mentioned that CNS metastases is often an exclusion criteria when conducting phase 2 studies. Please see the transcript for details of the subcommittee's discussion.*

3. **DISCUSSION:** 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.

**Committee Discussion:** *The subcommittee agreed that robust historical data for diffuse intrinsic pontine gliomas (DIPG) would be sufficient to conduct a prospective trial that compares clinical outcomes such as overall survival. Moreover, a subcommittee member commented that a comparator arm would not be needed and the historical controls could be*

*used to isolate the effect of ONC201. One member mentioned the additive effect with radiation therapy as a consideration. Please see the transcript for details of the subcommittee's discussion.*

4. **DISCUSSION:** 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 (e.g., patients younger than 2 years of age are ineligible in ongoing Study ONC014).

**Committee Discussion:** *The subcommittee agreed that there is no current evidence for toxicities in younger patients and that patients younger than 2 years of age should not be excluded. One member noted that patients greater than 3 years of age have a different prognosis and more historical control data than patients less than 3 years of age and that needs to be considered in trial design. One member addressed a potential contributing factor to exclusion is formulation, given that pediatric patients, specifically in the DIPG context, could have swallowing dysfunction. This member encouraged development of a non-pill formulation. Additionally, a member stated the need for a defined dose for younger patients in clinical studies even if older patients were included in the study population. Please see the transcript for details of the subcommittee's discussion.*

5. **DISCUSSION:** 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.

**Committee Discussion:** *The subcommittee agreed that for DIPG, a robust historical control could be utilized as a comparator and that a potential endpoint could be overall survival. Another member commented that single agent activity could be studied, such as in neuroblastomas and other tumors. The member further stated that preclinical signals could then be identified and help serve as a guide for future trial development. Another member discussed the potential for a trial design that allowed patients to receive radiation therapy after receiving the test drug, given the current data on combination therapies. Please see the transcript for details of the subcommittee's discussion.*

The meeting on June 20, 2019 was adjourned at approximately 2:30 p.m.