Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Meeting
June 16, 2023

Location: Please note that due to the impact of the COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topic: The subcommittee discussed considerations related to dosage optimization of new drug and biological products for pediatric patients with cancer. Dosage optimization is an integral aspect of oncology drug development and is important to maximizing the safety, efficacy, and tolerability of new drugs for pediatric cancers. Unique considerations associated with dosage selection and optimization in pediatric oncology include variability in pharmacokinetic and pharmacodynamic parameters by age and size, the need for age-appropriate formulations, potential for toxicities associated with long-term use, and the rarity of pediatric cancers. Representatives from the European Medicines Agency, the pediatric oncology investigator community, and the pharmaceutical industry were also invited to present.

These summary minutes for the June 16, 2023 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC) of the Food and Drug Administration were approved on August 18, 2023.

I certify that I attended the June 16, 2023 meeting of the pedsODAC of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Takyiah Stevenson, PharmD	Alberto S. Pappo, MD
Acting Designated Federal Officer, pedsODAC	Chairperson, pedsODAC

Final Summary Minutes of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Meeting
June 16, 2023

The Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on June 16, 2023. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary members were provided the briefing materials from the FDA. The meeting was called to order by Alberto S. Pappo, MD (Chairperson). The conflict of interest statement was read into the record by Takyiah Stevenson, PharmD (Acting Designated Federal Officer). There were approximately 331 people viewing the meeting. There was one Open Public Hearing (OPH) speaker presentation.

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

Agenda: The subcommittee discussed considerations related to dosage optimization of new drug and biological products for pediatric patients with cancer. Dosage optimization is an integral aspect of oncology drug development and is important to maximizing the safety, efficacy, and tolerability of new drugs for pediatric cancers. Unique considerations associated with dosage selection and optimization in pediatric oncology include variability in pharmacokinetic and pharmacodynamic parameters by age and size, the need for age-appropriate formulations, potential for toxicities associated with long-term use, and the rarity of pediatric cancers. Representatives from the European Medicines Agency, the pediatric oncology investigator community, and the pharmaceutical industry were also invited to present.

Attendance:
ODAC Members Present: David E. Mitchell (Consumer Representative); Alberto S. Pappo, MD (pedsODAC Chairperson)

ODAC Members Not Present: Ranjana H. Advani, MD; Jaffer A. Ajani, MD; Mark R. Conaway, PhD; Jorge A. Garcia, MD, FACP; Pamela L. Kunz, MD; Christopher H. Lieu, MD; Ravi A. Madan, MD; Jorge J. Nieva, MD; Ashley Rosko, MD; Anthony D. Sung, MD; Neil Vasan, MD, PhD

ODAC Member Present (Non-Voting): Jonathan D. Cheng, MD (Industry Representative)

Temporary Members: Frank M. Balis, MD; Steven G. DuBois, MD; Julia Glade Bender, MD; E. Anders Kolb, MD; Theodore W. Laetsch, MD; Donna Ludwinski, BSChE (Patient Representative); Holly Meany, MD; Rajen Mody, MD, MS; Donald (Will) Parsons, MD, PhD; Malcolm A. Smith, MD, PhD; Yoram Unguru, MD, MS, MA, HEC-C

FDA Participants (Non-Voting): Richard Pazdur, MD; Martha Donoghue, MD; Elizabeth S. Duke, MD; LCDR Ruby Leong, PharmD; Stacy S. Shord, PharmD, BCOP, FCCP; Xiaofei Wang, PhD; Kristin Wessel, MD

Acting Designated Federal Officer (Non-Voting): Takyiah Stevenson, PharmD

Open Public Hearing Speaker: Sophia Phillips, MS (National Center for Health Research)

The agenda was as follows:

Call to Order	**Alberto S. Pappo, MD** Chairperson, pedsODAC
Introduction of Subcommittee and Conflict of Interest Statement	**Takyiah Stevenson, PharmD** Acting Designated Federal Officer, pedsODAC
Introductory Remarks	**Martha Donoghue, MD** Associate Director for Pediatric Oncology Oncology Center of Excellence Office of the Commissioner Office of Oncologic Diseases (OOD) Office of New Drugs (OND), CDER, FDA
FDA PRESENTATIONS	
FDA Perspective on Dosage Optimization in Pediatric Oncology	**Kristin Wessel, MD** Medical Officer Division of Oncology 2 OOD, OND, CDER, FDA **Ruby Leong, PharmD, LCDR, USPHS** Clinical Pharmacology Team Leader Division of Cancer Pharmacology I Office of Clinical Pharmacology Office of Translational Sciences, CDER, FDA
Dosage Optimization Considerations for Chimeric Antigen Receptor (CAR) T-Cell Products	**Xiaofei Wang, PhD** Clinical Pharmacology Reviewer Division of Clinical Evaluation General Medicine Office of Clinical Evaluation Office of Therapeutic Products Center for Biologics Evaluation and Research, FDA
Clarifying Questions	

GUEST SPEAKER PRESENTATIONS

Considerations Related to Dosage Optimisation of New Drug and Biological Products for Paediatric Patients with Cancer - European Regulatory Perspective	**Dominik Karres, MD** Scientific Officer Paediatric Medicines Office Scientific Evidence Generation Department Human Medicines Division European Medicines Agency (EMA) **Olga Kholmanskikh, MD, PhD** Clinical Assessor Federal Agency for Medicines and Health Products – Belgium Member, Oncology Working Party of the EMA Alternate, Committee for Advanced Therapies of the EMA
Pediatric Oncology Drug Development: Dose and Dose Optimization	**Elizabeth Fox, MD, MSCR** Member, Department of Oncology Senior Vice President Clinical Research Administration St. Jude Children's Research Hospital Vice-Chair, Pediatric Early Phase Trial Network and Developmental Therapeutics Committee Children's Oncology Group
Dosage Optimization of New Drug and Biological Products for Pediatric Patients with Cancer: A Perspective from the Biopharmaceutical Industry	**Samuel C. Blackman, MD, PhD** Co-founder and Head of Research and Development Day One Biopharmaceuticals, Inc.

Clarifying Questions

LUNCH

OPEN PUBLIC HEARING

Questions to the Subcommittee and Subcommittee Discussion

Closing Remarks **Martha Donoghue, MD**

ADJOURNMENT

Questions to the Subcommittee:

1. **DISCUSSION:** Discuss the unique considerations associated with dosage optimization in pediatric oncology.

   Committee Discussion: *The Subcommittee discussed several unique considerations associated with dosage optimization in pediatric oncology. Subcommittee members commented that the treatment of pediatric cancers has significantly evolved from the standard use of cytotoxic chemotherapy and that there has been a corresponding shift in the types of drugs under development for pediatric cancers. Members agreed that different approaches to study design are therefore needed to better evaluate dosages in pediatric patients. Some members suggested moving away from primarily using toxicity as an endpoint to inform dosing. One member recommended enriching the patient population to focus on patients with tumors harboring the target of the drug under study during early dose-finding and better utilizing pharmacokinetic and pharmacodynamic data, in addition to toxicity data, to identify the optimized dosage(s) of oncologic drugs for pediatric cancers. Other Subcommittee members noted that the limited availability of age-appropriate product strengths and pediatric formulations and the rarity of pediatric cancers add to the challenge of conducting dosage optimization studies. Members recommended that pediatric formulations should be made available earlier for those drugs that have a high potential for activity in selected pediatric tumors. One Subcommittee member indicated that the approach to extrapolation from adult data should take into account biological differences between adult and pediatric tumors. Another member cautioned that even small reductions in the activity of a particular drug, which can occur with a reduced dosage, may have substantial impacts on the ability to cure a particular cancer, and that it may be appropriate to dose escalate until a toxicity threshold is reached. One member highlighted the need for studying adverse effects caused by longer-term exposures, as some pediatric oncology drugs are given chronically. Another member emphasized the importance of studying combinations early, perhaps during the first-in-pediatric trial in some cases. Members agreed that more extensive dosage optimization should be reserved for drugs that have demonstrated sufficient antitumor activity to support continued, larger-scale development in pediatric patients. Please see the transcript for details of the Subcommittee's discussion.*

2. **DISCUSSION:** Discuss the potential challenges to identifying an optimized dosage for new drugs and biological products for pediatric cancers and potential strategies to address these challenges.

   Committee Discussion: *Some Subcommittee members agreed that conducting post-marketing studies could be a potential strategy to address challenges with identifying an optimized dosage for new drugs and biological products for pediatric cancers. One member stated that for the antibody-drug conjugate (ADC) class of drugs, extensive dosage optimization may not be needed for pediatric patients given the availability of information on antitumor activity and tolerability obtained in adult patients at various dosages. Another member commented that characterizing the dose response curves of new drugs and biologics for pediatric cancers may pose additional challenges because the starting dose in pediatrics is generally a dose known to be therapeutic in adults and successive dose increases are relatively small,*

and that the strategy of intra-patient dose escalation may be helpful in some cases. Please see the transcript for details of the Subcommittee's discussion.

3. **DISCUSSION:** For drugs and biological products being developed in both adult and pediatric patients with cancer, consider how the timing of dosage selection in adults impacts the timing of trial initiation and dosage optimization in pediatric patients with cancer.

   Committee Discussion: *The Subcommittee agreed that the timing of identification of the optimized dosage in adults should not delay trial initiation and dosage optimization in pediatric patients with cancer. Some Subcommittee members commented that there is an ethical obligation for early initiation of pediatric clinical trials of drugs using a dosage that can provide the prospect of benefit. Subcommittee members indicated that the toxicity profile of cancer agents observed in adults should be taken into consideration in initial pediatric dosage selection; however, members acknowledged that the toxicity profiles between adult and pediatric populations may differ for a variety of reasons, including the extent of prior therapy. One Subcommittee member advocated designing initial trials that enroll a small number of pediatric patients to determine whether there is sufficient antitumor activity to warrant more extensive dosage optimization, which should also consider pertinent information obtained in adult patients with cancer. One member suggested re-examining whether eligibility criteria should be broadened, for example not requiring patients to have exhausted all other alternative therapies, which can delay access to clinical trials. Another member commented that since the drug exposures needed for antitumor activity in pediatric patients is generally not lower than the exposures needed in adults, obtaining real-time pharmacokinetic data to determine whether target exposures are being reached can be helpful during initial dose-finding trials to facilitate timely dose-escalation decision-making. Please see the transcript for details of the Subcommittee's discussion.*

4. **DISCUSSION:** Discuss the considerations for dosage optimization in pediatric oncology clinical trials investigating combination therapies.

   Committee Discussion: *One Subcommittee member commented that both schedule optimization and dose optimization are important considerations in pediatric oncology clinical trials investigating combination therapies. The member noted that there are examples of when sequential dosing of drugs is better tolerated than concomitant administration of drugs in a combination therapy. Some Subcommittee members mentioned the importance of maintaining the efficacy of established drug combinations when a new drug is added to the combination and that the potential for overlapping toxicities should be considered. Subcommittee members agreed that studying the tolerability of combining drugs at their full, effective dosages is important. One member added that evaluating tolerability of combination therapies is logistically less challenging than determining optimal dosages of multiple combinations of drugs across a variety of indications. Others advocated dedicating more resources to obtaining pharmacokinetic information in trials studying combinations in order to optimize dosages of new drugs when they are used in combination. Another member noted that some patients may receive combination therapies chronically and that long-term and cumulative toxicities are additional important considerations in clinical trials*

investigating combination therapies. Please see the transcript for details of the Subcommittee's discussion.

The meeting was adjourned at approximately 2:50 p.m. ET on June 16, 2023.