



## Waiver to Allow Participation in a Food and Drug Administration Advisory Committee

DATE: June 22, 2016

TO: Jill Hartzler Warner, J.D.  
Associate Commissioner for Special Medical Programs, FDA

THROUGH: Michael F. Ortwerth, Ph.D.  
Director, Advisory Committee Oversight and Management Staff  
Office of Special Medical Programs

FROM: Jayne E. Peterson  
Director, Division of Advisory Committee and Consultant Management  
Office of Executive Programs  
Center for Drug Evaluation and Research

**Name of Advisory Committee Member:** Alberto Pappo, M.D.

**Committee:** Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (PedsODAC)

**Meeting Date:** June 28-29, 2016

### **Description of the Facts on Which the Waiver is Based:**

The Best Pharmaceuticals for Children Act of 2002 (BPCA) expressly charged that the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (PedsODAC), a subcommittee of the Oncologic Drugs Advisory Committee (ODAC) shall: (A) evaluate and, to the extent practicable, prioritize new and emerging therapeutic alternatives available to treat pediatric cancer; (B) provide recommendations and guidance to help ensure that children with cancer have timely access to the most promising new cancer therapies; and (C) advise on ways to improve consistency in the availability of new therapeutic agents. (Pub. Law 107-109, Section 15(a)(1)).

The role of the Pediatric Subcommittee is legislated by BPCA. Notably, the PedsODAC does not provide advice to FDA with respect to approval of any specific product for any specific pediatric cancer indication. The Office of Hematology and Oncology Products in the Center for Drug Evaluation and Research brings issues related to approval of any product for a cancer indication, including any pediatric cancer indication, to the ODAC, not the PedsODAC.

The cancers of adults and children are very different and although the outcome for children with cancer has improved dramatically during the past several decades, cancer remains the leading

cause of death from disease in children. Those children who survive often do so at an enormous cost associated with the long term and late effects of existing therapy, which are frequently debilitating. Thus, there is an urgent need for new drugs and biologic products for the treatment of childhood cancer.

Pediatric cancer drug development is complex and very different from drug development in other disease areas and is largely dependent upon cancer drug discovery and development in adults. Early consideration of new promising agents for study in children is critical to timely development of new treatments. On June 28-29, 2016, the PedsODAC will meet to discuss five chemical entities in various stages of development for adult cancer indications to assess their relevance for possible development for use in one or more pediatric cancers. The subcommittee will consider and discuss issues concerning possible pediatric cancers and stages of disease to be studied, patient populations to be included, and possible designs of clinical trials to expedite early evaluation to facilitate the development of these chemical entities as potential new drugs for use in pediatric cancer. The discussions may also provide information to FDA pertinent to the formulation of Pediatric Written Requests (PWRs), if appropriate.

Because pediatric cancer care is very closely integrated with pediatric cancer clinical research and new drug development, all children with cancer are treated at academic centers, and nearly all of these centers are members of a National Cancer Institute-funded clinical trials network. As a result, the experts are invariably researchers at these institutions. The expertise that FDA seeks cannot be found outside of this context. The insights the Agency seeks can be provided only by learned researchers with extensive experience with studies of investigational agents in the pediatric age group. These investigators generally *do not derive substantial personal financial benefit* from industry grants and contracts to their institutions, and their institutions receive the industry funds necessary to offset institutional costs for patient care and other institutional clinical research costs.

#### Description of the Particular Matter to Which the Waiver Applies

On June 28-29, 2016, information will be presented to the subcommittee to elicit discussion and advice on potential pediatric development plans for five chemical entities, including LOXO-101, entrectinib, and tazemetostat.

Alberto Pappo, M.D., is Director of the Solid Tumor Division and Co-Leader of the Developmental Biology and Solid Tumor Program at St. Jude Children's Research Hospital. He has not identified any personal financial interests that are likely to be affected by the particular matters to be discussed at the subcommittee meeting. However, he has identified financial interests of his employer, which are imputed to him under a federal conflict of interest statute, 18 U.S.C. § 208. The financial interests to which this waiver applies are the imputed financial interests related to (1) LOXO-101, sponsored by Loxo Oncology, and (2) tazemetostat, sponsored by Epizyme, Inc. Tazemetostat will be discussed in Session 1 of this meeting; LOXO-101 will be discussed in Session 4 of this meeting; Entrectinib, a chemical entity with similarities to LOXO-101 in its mechanism of action, is at issue for Session 5 of this meeting.

The total funding to St. Jude is anticipated to be between \$50,001 – 100,000 per year.

### Type, Nature, and Magnitude of the Financial Interest(s)

Dr. Pappo's employer, St. Jude Children's Research Hospital is participating in a clinical study funded by Loxo Oncology titled "A Phase 1 Study of the Oral TRK Inhibitor LOXO-101 in Pediatric Patients With Advanced Solid or Primary Central Nervous System Tumors." This is an open-label, dose-escalation trial of LOXO-101. Dr. Pappo is serving as Sub-Investigator and he provided input into the development of the trial.

The total funding to St. Jude is anticipated to be between \$50,001 – 100,000 per year if the target number of patients is reached. The study started April 13, 2016 and is anticipated to continue for four years dependent upon patient accrual. These funds are intended to offset the costs for (1) patient care that is not necessary as part of standard medical care and is performed solely for research purposes (for example, laboratory studies and radiographic imaging procedures as well as associated nursing and pharmacy costs for investigational drug preparation, storage, accounting, and administration); (2) abstracting, collecting, and submitting clinical, laboratory, and radiographic data on detailed Case Report Forms to a centralized data management center; and (3) associated auditing of source documents and submitted data.

In addition, Dr. Pappo's employer is currently negotiating with Epizyme Inc., for a study titled, "A Phase 1 Study of the EZH2 Inhibitor Tazemetostat in Pediatric Subjects with [REDACTED] (b) (4) [REDACTED]" Dr. Pappo will be listed internally at St. Jude Children's Research Hospital (SJCRH) as a Co-Investigator. In SJCRH terminology, the Co-Investigator designation is given to any physician who is authorized to enroll a patient in a specific clinical trial; for this trial, all solid tumor and brain tumor physicians practicing at St. Jude's have been assigned the role of Co-Investigator. The SJCRH internal Co-Investigator role is not the same as a study Principal Investigator or study Co-Principal Investigator role as they are not listed on the study contract.

The total funding to St. Jude's from this study is anticipated to be between \$0 – 50,000 per year. The duration of the study is expected to last five years dependent upon patient accrual. Dr. Pappo ***will not receive any salary support*** or personal remuneration for his involvement.

### Basis for Granting the Waiver

As discussed in more detail below, the waiver is supportable for a number of reasons. The financial interests at issue are small, particularly for a research institution the size of Dr. Pappo's employer. Dr. Pappo's research at St. Jude is not closely related to the advisory committee discussions, which will focus on the potential for demonstrating efficacy of products in pediatric cancer patients. Finally, the subject of this meeting requires the participation of individuals with a wide ranging knowledge of pediatric oncology and requires a rare level of expertise. Dr. Pappo has significant experience with this subject matter and has effectively led past PedsODAC meetings.

*The financial interests are small, and the research is not closely related to the advisory committee discussion: the discussion will not culminate in a vote.*

As noted above, it is expected that the total funding to St. Jude's under the LOXO-101 and Epizyme studies will be between \$50,001 – 150,000 per year. This is a very small amount of money for a research institution such as Dr. Pappo's employer. According to the Combined Statements of

Financial Position disclosed by St. Jude, assets are of approximately \$4 billion dollars, of which an estimated \$16 million is received from grants and contracts.<sup>1</sup>

In its February 23, 2007, Memorandum to Designated Agency Ethics Officials regarding Waivers Under 18 U.S.C. § 208, the Office of Government Ethics has provided guidance in determining whether the need for an individual's services on an advisory committee outweighs the potential for a conflict of interest created by the disqualifying financial interest. This guidance provides that the responsible official should consider the dollar value of the potential gain or loss that may result from participation in a particular matter – “Although an important factor to consider, the value of the potential gain or loss often may be only an estimate. Furthermore, depending on the type of interest affected, it may be difficult to estimate. For example, it would be simpler to estimate the value of the potential gain that a decision to award a \$1 million contract would have on a relatively small company, compared to the impact of the same award on a Fortune 500 company. Of course, the greater the potential gain or loss, the more unlikely it is that a waiver can be justified.”<sup>2</sup> A consideration of the financial interests at issue here leads us to conclude that the interests are not so great that a waiver could not be justified.

The PedsODAC meeting is meant to elicit discussion of the data currently available from adult studies and whether there is any pediatric cancer type for which there is an unmet clinical need that these chemical entities might address. The PedsODAC meeting will focus on preliminary discussions and general considerations in pediatrics, including discussions around molecular abnormalities, about potential indications that might be feasible for the drug substances, and about international collaborative efforts. Significantly, the advisory committee members will not recommend approval or disapproval of any particular product. Such recommendations would be grossly premature and simply could not be made at this early stage in product development. The majority of oncology products studied in the phase 1 setting in children do not proceed through development to submission and approval of a new drug application. Very few chemical entities in these early stages of evaluation and development ever proceed to a marketing application.

Moreover, the role of the PedsODAC is not to provide any advice to the Agency with respect to approval of any specific product for any specific pediatric cancer indication. Any recommendations to FDA with respect to approval of any product for a cancer indication are provided by the ODAC, and not the Pediatric Subcommittee.

*The meeting requires a wide knowledge of pediatric oncology and subspecialties, and expertise in designing clinical trials.*

To meet statutory responsibilities to evaluate and prioritize new and emerging therapeutic alternatives to treat pediatric cancer and to provide recommendations and guidance to help ensure that children with cancer have timely access to the most promising new cancer therapies, this meeting of the PedsODAC requires the participation of experts with a wide and deep knowledge of pediatric oncology and product development. Such experts typically develop their knowledge through their work at centers of excellence for the treatment of pediatric cancers, the very sites where investigational drugs are studied. This is particularly true for experts in rare pediatric

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<sup>1</sup> See Combined Financial Statements as of and for the Years Ended June 30, 2015 and 2014, and Independent Auditors Report. Available at [https://www.stjude.org/content/dam/en\\_US/shared/www/about-st-jude/financial-information/combined-sjcrh-alsac-audited-financial-statements-fy15.pdf](https://www.stjude.org/content/dam/en_US/shared/www/about-st-jude/financial-information/combined-sjcrh-alsac-audited-financial-statements-fy15.pdf). (Accessed: June 9, 2016)

<sup>2</sup> See Page 9 of the OGE Memo on Waiver Under 18 U.S.C. §208. Available at [https://www.oge.gov/Web/OGE.nsf/All+Advisories/328CE4B5A300EAE85257E96005FBDE5/\\$FILE/do-07-006.pdf?open](https://www.oge.gov/Web/OGE.nsf/All+Advisories/328CE4B5A300EAE85257E96005FBDE5/$FILE/do-07-006.pdf?open). (Accessed: June 9, 2016)

cancers; patients frequently must travel to be treated by a physician with experience in a particular rare cancer.

Dr. Pappo is considered one of the world's leading expert on rare pediatric cancers. He received his medical degree from the Medical School, Universidad Anahuac, Mexico City, and completed his residency at the University of Texas Health Science Center. His subspecialties include sarcoma, melanoma, and gastrointestinal pediatric oncology. Dr. Pappo is the only meeting participant with expertise in the rare childhood cancers for which some of the products being discussed may be relevant. Dr. Pappo has extensive knowledge and experience in current standard approaches to studying and treating these diseases. His expertise is critical to the committee as it considers the potential for benefit in studying these drugs in children. In the interest of public health, it is critical that FDA have available the unique expertise that Dr. Pappo will provide for the discussion of the particular matters before the committee.

*Relevant expertise is concentrated in the institutions comprising the children's oncology group, and other candidates with the necessary expertise have not been found.*

Given the relative rarity of childhood cancer, collaboration and concentration of expertise are essential. This is particularly true for rare pediatric cancers, which most pediatric oncologists would never see, or may see only once in a lifetime of practice. Although the majority of adult patients with cancer are cared for in the community and enroll in clinical trials at a rate of only 3%, nearly all children with cancer are treated at academic centers, and the vast majority are enrolled in clinical trials. Nearly all of these academic centers are members of the Children's Oncology Group (COG), a National Cancer Institute-funded clinical trials network of more than 230 pediatric institutions throughout the United States, Canada, and other foreign sites.

Pediatric cancer care is very closely integrated with pediatric cancer clinical research and new drug development. The COG and its predecessor cooperative groups have a more than 50-year history. Cooperation and collaboration in the design and conduct of clinical trials over this period of time has changed childhood cancer from a nearly uniformly fatal disease to one where more than 85% are cured. But, despite the dramatic increase in cure rates, cancer remains the major cause of children's death from disease in the United States and other developed countries. Cure often comes at a substantial cost in the form of severe and often debilitating late effects due to toxicity of therapy. Development of new cancer therapies remains a pressing need.

Industry sponsors work closely with investigators and institutional members of the COG, which employ the most expert researchers. In fact, definitive licensing studies, incorporating randomized controlled trial design, are generally only conducted within the COG and its clinical trial infrastructure, which is federally funded for NIH/NCI approved research. Reimbursement for this federally funded infrastructure is provided by industry sponsors in the form of per case reimbursement.

More than 90% of pediatric cancer patients in the United States are treated at COG institutions and most are enrolled in clinical trials. Of the approximately 230 COG institutions, a much smaller number of institutions (up to about 50, including St. Jude's) are involved in early clinical trials of drugs to treat rare pediatric cancers. These institutions employ researchers with the highest levels of expertise in pediatric cancers and drug development, the very experts FDA needs to hear from on the issues before the PedsODAC.

Although efforts were taken to seek out individuals with the least potential for a conflict of interest, for the reasons noted above, finding experts for this meeting has been challenging. Approximately 95% of the experts with the expertise and experience needed are affiliated with

COG institutions. Due to their expertise, qualified candidates face many demands on their time. In fact, eight other individuals with expertise in Pediatric Oncology and Pediatric Hematology were contacted but were unable to attend due to scheduling conflicts.

*Dr. Pappo has been an effective Chair.*

Dr. Pappo has served as the Chair for most recent meetings of the PedsODAC, and he has very deftly led these subcommittee discussions. He is the only member of the June 28-29 committee who has chaired a PedsODAC. He brings additional background and knowledge as one of only two standing members from the parent ODAC committee who will be attending this subcommittee meeting.

Accordingly, I recommend that you grant a waiver for Dr. Alberto Pappo, a member of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee, from the conflict of interest prohibitions of 18 U.S.C. § 208(a).

Certification:

  X   The individual may participate, pursuant to 18 U.S.C. 208(b)(3) – The need for the individual’s services outweighs the potential for a conflict of interest created by the financial interest involved.

Limitations on the Special Government Employee’s Ability to Act:

           Non-voting

           Other (specify):

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           Denied – The individual may not participate.

           /S/  
Jill Hartzler Warner, J.D.  
Associate Commissioner for Special  
Medical Programs

           6/24/16  
Date