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

DATE: May 21, 2020

TO: Russell Fortney
Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist

FROM: Byron Marshall
Director, Division of Advisory Committee and Consultant Management
Office of Executive Programs
Center for Drug Evaluation and Research

Name of Advisory Committee Meeting Temporary Voting Member: **Ira Dunkel, M.D.**

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

Meeting date: June 17-18, 2020

Description of the Particular Matters to Which the Waiver Applies:

The Best Pharmaceuticals for Children Act of 2002 (BPCA) expressly charged that the 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 Oncologic Diseases 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 17, 2020, information will be presented regarding pediatric development plans for two products that are in development for an adult oncology indication. The subcommittee will consider and discuss issues relating to the development of each product for pediatric use and provide guidance to facilitate the formulation of written requests for pediatric studies, if appropriate. The two products under consideration are: (1) SP 2577 application presentation by Salarius Pharmaceuticals, Inc. and (2) Marizomib, application presentation by Celgene International II Sàrl, a wholly owned subsidiary of Bristol-Myers Squibb

On June 18, 2020, information will be presented regarding pediatric development plans for two products that are in development for an adult oncology indication. The subcommittee will consider and discuss issues relating to the development of each product for pediatric use and provide guidance to facilitate the formulation of written requests for pediatric studies, if appropriate. The two products under consideration are: (1) CD30.CAR-T, application presentation by Tessa Therapeutics and (2) SNDX-5613, application presentation by Syndax Pharmaceuticals, Inc.

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.

Dr. Dunkel is serving as a temporary voting member of the PedsODAC. He has been invited to participate in the June 17--18, 2020, PedsODAC meeting. The particular matters described above to be discussed during the meeting are particular matters involving specific parties.

Type, Nature, and Magnitude of the Financial Interests:

Dr. Dunkel is an Attending Physician at Memorial Sloan Kettering Cancer Center (MSKCC), and Chair of the Pediatric Brain Tumor Consortium (PBTC). He has identified personal interests and interests from MSKCC and the PBTC which are imputed to him under the federal conflict of interest statute, 18 U.S.C. § 208, that can be affected by the particular matter that is the subject of the subcommittee meeting.

Dr. Dunkel consults for (b) (4) as a member of the pediatric oncology steering committee. In this role he can be asked to consult on any pediatric cancer, including cancers under consideration at the upcoming meeting. This consulting agreement began in December 2018 and is expected to run until February 2021. Dr. Dunkel receives approximately $0 - $5,000 per year in personal remuneration.

Starting in May 2020, Dr. Dunkel began consulting for (b) (4) as a member of the pediatric advisory council. This consulting agreement is expected to run until May 2021. In this role he can be asked to consult on any pediatric cancer, including cancers under consideration at the upcoming meeting. Dr. Dunkel receives approximately $0 - $5,000 per year in personal remuneration.

Dr. Dunkel consults for (b) (4) for pediatric brain tumors. His consulting role began in May 2017 and has no expected end date. Dr. Dunkel receives approximately $0 - $5,000 per year in personal remuneration. Indications before the advisory committee, including DIPG, have been the subject of his consulting work for (b) (4)

Starting in October 2019, Dr. Dunkel began consulting for (b) (4) on pediatric oncology. This consulting agreement is expected to run until October 2021. Dr. Dunkel receives approximately $10,001 - $25,000 per year in personal remuneration. Dr. Dunkel's work with (b) (4) is expected to relate to drug products and cancer types that will be discussed during the upcoming advisory committee meeting.

MSKCC has a contract for a Bristol-Myers Squibb sponsored study titled: Phase IB/II Clinical Trial of Nivolumab Monotherapy and Nivolumab in Combination with Ipilimumab in Pediatric Subjects with High Grade Primary CNS Malignancies" (NCT03130959). The purpose of this study is to determine the safety and effectiveness of nivolumab alone and in combination with ipilimumab in pediatric patients with high grade primary central nervous system malignancies. Dr. Dunkel is Chair of the Scientific Committee for this study. This study has been ongoing since 2017 and is expected to last until June 2021. The total funding for this study, to MSKCC, is anticipated to be between $ (b) (4) per year. Dr. Dunkel receives approximately $10,001 - $25,000 per year in salary support. Some DIPG patients have been enrolled in the study.

Dr. Dunkel serves as Chair of the PBTC, a multidisciplinary cooperative research organization devoted to the study of correlative tumor biology and new therapies for childhood tumors. The PBTC was formed by the National Cancer Institute at the National Institutes of Health in 1999 to improve treatment options for children with brain tumors. Dr. Dunkel's salary at MSKCC is partially supported by the PBTC. Dr. Dunkel reported the following PBTC studies that are related to the particular matters to be discussed at the upcoming meeting:

> PBTC-051: MSKCC has a contract with the PBTC which has an agreement with Apexigen for a study titled: Phase I Study to Evaluate the Safety and Tolerability of the CD40 Agonistic Monoclonal Antibody APX005M in Pediatric Subjects with Recurrent/Refractory Brain Tumors and Newly Diagnosed Brain Stem Glioma (NCT03389802). Dr. Dunkel is the Principal Investigator at MSKCC for this study. The

study began in November 2017 and is ongoing until September 2022. Funding for this study to PBTC from Apexigen, is anticipated to be between $ (b) (4) per year. The funding from PBTC to MSKCC is estimated to be between $ (b) (4) per year. This study is for a general indication that encompasses DIPG.

PBTC-042: A Phase I study of CDK 4-6 inhibitor PD- 0332991 (palbociclib; IBRANCE) in children with recurrent, progressive or refractory central nervous system tumors (NCT02255461). The study began in October 2014 and is ongoing with no established end date. Funding for this study from Pfizer to the PBTC is anticipated to be between (b) (4) per year. This study is for a general indication that encompasses DIPG, and is closed to accrual (no additional subjects will be enrolled) but remains open for data analysis

PBTC-043: A Phase I Trial of Pomalidomide for children with recurrent, progressive or refractory CNS tumors (NCT02415153). The study began in July 2015 and is ongoing with no established end date Funding from Celgene to the PBTC is anticipated to be between (b) (4) per year. This study is for a general indication that encompasses DIPG, and is closed to accrual but remains open for data analysis

PBTC-047: A Phase I Trial of Panobinostat in Children with Diffuse Intrinsic Pontine Glioma (NCT02717455). The purpose of the study is to study the side effects and best dose of panobinostat in treating younger patients with DIPG. Novartis provides panobinostat for the study. The study began in March 2016 and is ongoing until October 2023. Funding for this study from Novartis to the PBTC is anticipated to be between (b) (4) per year; additional funds from the Lylas Nsouli Foundation to the PBTC are anticipated to be between (b) (4) per year. This study involves a competing product for an indication, DIPG, to be discussed at the upcoming meeting.

PBTC-048: A Feasibility Trial of Optune for Children with Recurrent or Progressive Supratentorial High-Grade Glioma and Ependymoma (NCT03033992). The study began in January 2017 and is ongoing until April 2021. Funding from Novocure to the PBTC is anticipated to be between (b) (4) per year. This study involves one of the indications before the advisory committee (HGG).

PBTC-050: A Phase I and Surgical Study of Ribociclib and Everolimus (RAD001) in Children with Recurrent or Refractory Malignant Brain Tumors (NCT03387020). The study began in January 2018 and is ongoing until July 2020. Funding from Novartis to the PBTC for this study is anticipated to be between (b) (4) per year. This study is for a general indication that encompasses DIPG, and is closed to accrual but remains open for data analysis

PBTC-055: A Phase I/II trial of Dabrafenib, Trametinib, and Hydroxychloroquine (HCQ) for BRAF V600E-mutant or Trametinib and HCQ for BRAF fusion/duplication positive or NF1-associated recurrent or progressive gliomas in children and young adults (NCI-2019-06216). The study began in January 2018 and is ongoing until February 2027. Funding

from the PBTC for this study is anticipated to be between (b) (4) per year. This study involves an indication to be discussed at the upcoming meeting.

Basis for Granting the Waiver:

Dr. Dunkel has unique qualifications and specialized expertise needed for this particular matter.

Unlike AC meetings focused on a product and indication, this meeting will be a scientific collaboration on the currently available data to gain information that could inform the formulation of a Written Request, if appropriate. 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.

Dr. Ira Dunkel is a Pediatric Oncologist at Memorial Sloan Kettering Cancer Center, Professor of Pediatrics at Weill Cornell Medical College, and Attending Pediatric Oncologist at Memorial Hospital and New York Presbyterian Hospital. He received his undergraduate degree from Johns Hopkins University and his medical degree from Duke University School of Medicine in 1985 and has been practicing for more than 30 years. He completed his pediatric residency at Duke and spent one year as a fellow in pediatric infectious diseases, both at Duke and at Muhimbili Medical Center in Dar-es-Salaam, Tanzania. He completed a pediatric hematology-oncology fellowship at the Memorial Sloan Kettering Cancer Center and New York Hospital. His main research interests are in the fields of Pediatric Neuro-oncology, Retinoblastoma, and Developmental Therapeutics and he has published more than 140 peer-reviewed papers. He is currently Chair of the Pediatric Brain Tumor Consortium and a member of the National Cancer Institute's Brain Malignancy Steering Committee. Industry sponsors work closely with investigators at institutions, which employ the most expert researchers, such as Dr. Dunkel. 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. There is a need for pediatric oncology subspecialties to discuss the rare cancers for which these products may be a good match. Brain tumors represent a major unmet clinical need in children which makes Dr. Dunkel's participation critical.

The particular matter is not sensitive.

The meeting topics are not considered sensitive and the FDA Division with responsibility for the products to be discussed at the upcoming meeting does not expect that the meeting is likely to receive significant public interest, (non-trade) press interest, nor is it considered highly controversial. Moreover, the discussion at the meeting will be only one source of information for

the Agency's plans related to the submission of a Written Request for evaluating these drugs in children.

Dr. Dunkel's expertise in this particular matter is necessary in the interest of public health.

On June 17-18, 2020, the subcommittee will meet to discuss SP 2577, marizomib, CD30.CAR-T, and SNDX-5613 which are in early stages of development. The pediatric cancers that will be discussed for these products will include, but are not limited to, Ewing sarcoma, DIPG, a type of brain tumor, classical Hodgkin lymphoma, and Mixed Lineage Leukemia (MLL) gene rearranged acute leukemia. Ewing sarcoma is a rare bone tumor that occurs most often in adolescents; it is a very rare cancer in adults. The National Institutes of Health reports that Ewing sarcoma accounts for about 1.5 percent of all childhood cancers, and it is the second most common type of bone tumor in children. The potential use of marizomib in Ewing sarcoma is in the context of recurrent/relapsed disease, for which no curative therapies currently exist, therefore, the need for new therapies represents a particularly dire, unmet clinical need. DIPG accounts for 10 percent of all childhood central nervous system tumors. Approximately 300 children in the United States are diagnosed with DIPG each year. No effective drugs have been developed for this disease. The current treatment is limited to radiotherapy, and with radiotherapy, median survival for children with DIPG is only 9 to 11 months. Even drugs in early development have failed to yield robust efficacy signals. Relapsed/refractory classical Hodgkin lymphoma is a malignant lymphoma that accounts for approximately 7 percent of childhood cancers and 1 percent of childhood cancer deaths in the United States. The American Cancer Society reports that classical Hodgkin lymphoma (cHL) accounts for more than 9 in 10 cases of Hodgkin lymphoma in developed countries and comprises 6% of childhood cancers. Approximately 90% to 95% of children with Hodgkin lymphoma can be cured, prompting increased attention to devising therapy that lessens long-term morbidity for these patients. Aggressive leukemias arise in both children and adults as a result of rearrangements to *MLL* genes and are associated with both acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL). The MLL gene is frequently rearranged through chromosomal translocations, most notably in >70% of cases of infant leukemia with 5.2% of all the AML cases and in 22% of all the ALL cases. Whereas treatment of non-mixed lineage leukemia in children has become the textbook success story of modern medicine, with 5-year survival rates approaching 90%, mixed lineage leukemia treatment seems to have hit a roadblock with hardly 40% of all infants surviving five years after diagnosis. Patients with *MLL* rearrangements not only have poorer prognosis, but they also have shorter event free and overall survival rates. They do not respond at all well to the standard therapies for ALL (acute lymphoblastic or lymphocytic leukemia) and often suffer from early relapse after chemotherapy. Therefore, new treatment modalities are urgently needed. Recent advances have begun to reveal the molecular mechanisms driving MLL associated leukemias, which provide opportunities for therapeutic development. Therefore, in the interest of public health, it is critical that FDA have available the unique expertise that Dr. Dunkel will provide the committee.

Any potential for a conflict of interest is greatly outweighed by the strong need for Dr. Dunkel's expertise in this matter.

The PedsODAC meeting is meant to elicit discussion of the data currently available. The advisory committee members will not recommend approval or disapproval of this product. 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 cancers; patients frequently must travel to be treated by a physician with experience in a particular rare cancer. Multiple pediatric oncologists, each with specific sub-specialty expertise and with internationally recognized expertise in pediatric cancer drug development are needed for this meeting given the multiplicity of clinical indications to be considered. The complexity of clinical study design and conduct in rare pediatric cancer populations requires multiple clinical and scientific perspectives.

Dr. Dunkel is a world class pediatric neuro-oncologist and directs one of the largest pediatric brain tumor programs in the world. Dr. Dunkel chairs the NCI-funded Pediatric Brain Tumor Consortium. He is an internationally recognized pediatric neuro-oncologist with notable experience and expertise in early phase clinical investigations.

Accordingly, I recommend that you grant Dr. Ira Dunkel, a temporary voting member of the Pediatric Oncology Subcommittee of the Oncology Drugs Advisory Committee, a waiver from the conflict of interest prohibitions of 18 U.S.C. § 208(a).

Certification:

___✓___ 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 Regular Government Employee's or Special Government Employee's Ability to Act:

_____ Non-voting

_____ Other (specify):

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_____ Denied – The individual may not participate.

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June 1, 2020

Russell Fortney
Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist

Date