



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

DATE: April 3, 2013

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

THROUGH: Vince Tolino _____ /s/
Director, Ethics and Integrity Staff
Office of Management Programs
Office of Management

Michael F. Ortwerth, Ph.D. _____ /s/
Director, Advisory Committee Oversight and Management Staff
Office of Special Medical Programs

FROM: Jayne E. Peterson _____ /s/
Director, Division of Advisory Committee and Consultant Management
Center for Drug Evaluation and Research

SUBJECT: Conflict of Interest Waiver for Takami Sato, M.D., Ph.D.

Name of Advisory Committee Member (Temporary Voting Member): Takami Sato, M.D., Ph.D.

Committee: Oncologic Drugs Advisory Committee (ODAC)

Meeting date: May 2, 2013

Description of the Facts on Which the Waiver is Based:

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

Takami Sato, M.D., Ph.D., is Director, Metastatic Uveal Melanoma Program, Department of Medical Oncology Kimmel Cancer Center, Jefferson Medical College of Thomas Jefferson University (TJU). TJU is _____^{(b) (4)} for a research contract with _____^{(b) (4)} _____, for a study of a competing product

Waiver to Allow Participation in a Food and Drug Administration Advisory Committee
May 2, 2013 Oncologic Drugs Advisory Committee Meeting
Takami Sato, M.D., Ph.D.

for treatment of (b) (4) the product being reviewed by the committee. Dr. Sato is the Principal Investigator for this ongoing study at TJU.

In addition, TJU is conducting an investigator-initiated clinical trial related to another product for (b) (4) the product being reviewed by the committee. Dr. Sato is Principal Investigator for this ongoing study. The product being studied is (b) (4) and the sponsor of the product is (b) (4) at this time. Further, this study is not expected to produce the data that would be needed to (b) (4). However, while the impact is likely to be minimal, the possibility cannot be excluded that the outcome of the pending new drug application for the Melblez Kit could impact the ongoing funding of Dr. Sato's study.

The magnitude of the financial interests:

Thomas Jefferson University is awarded between \$0-50,000 per year from (b) (4); and, between \$100,001 and \$300,000 per year for the second study described above.

Description of the Particular Matter to Which the Waiver Applies:

During the afternoon session, the committee will discuss new drug application (NDA) 201848 a drug/device combination product with the proposed trade name Melblez Kit [Melblez (Melphalan) for Injection for use with the Delcath Hepatic Delivery System], submitted by Delcath Systems, Inc. The proposed indication (use) for this product is for the treatment of patients with unresectable ocular melanoma that is metastatic to the liver.

Additional Facts:

The Melblez Kit contains a previously approved chemotherapy drug, melphalan, and a device for delivery of the drug by percutaneous hepatic artery infusion. The dose and route of administration of melphalan is novel; the placement of the device, which isolates the arterial blood supply of the liver for administration of the drug and filters the blood before it is released back to the general circulation, is conducted under general anesthesia in a surgical suite for placement and use of the device. This would be the first product drug/device combination approved by the Center for Drug Evaluation and Research specifically for the treatment of metastatic ocular melanoma and uses a novel endpoint as the basis for approval, hepatic progression-free survival (hPFS). The toxicity of this drug/device combination product is substantial, thus expert opinion will be needed to provide advice on the risk:benefit assessment and net clinical benefit of this product. The toxicity profile includes severe hypotension resulting in heart attack, stroke, and kidney failure, massive bleeding, and injury to gastrointestinal tract from the use of the device (procedural toxicities) in addition to severe and prolonged bone marrow suppression with risk of serious and fatal bacterial infections and liver injury from the drug administered.

Basis for Granting the Waiver:

Dr. Takami Sato is a nationally and internationally recognized expert in the treatment of uveal melanoma and in the use of devices for the delivery of liver-directed therapy for treatment of hepatic metastases. He received his M.D. and Ph.D. degrees from Jichi Medical University in Japan. Dr. Sato is currently the K.

Hasumi Professor of Medical Oncology in the Department of Medical Oncology, a graduate advisor in the Jefferson College of Graduate Studies, and since 2006 has served as the Director of the Metastatic Uveal Melanoma Program in the Department of Medical Oncology at Thomas Jefferson University. Dr. Sato also holds an appointment as a Consultant for Oncology at the Wills Eye Hospital (1993-present). In addition to his academic and administrative positions, Dr. Sato has published more than 50 articles in peer-reviewed journals including papers on the cytogenetic profile of ocular melanoma, the adjuvant treatment of melanoma, systemic treatment of metastatic cutaneous or ocular melanoma and a variety of liver-directed approaches for the treatment of hepatic metastases. His clinical experience encompasses systemic treatment with traditional cytotoxics, non-specific immunomodulatory agents, vaccines, and targeted agents as well as liver-directed therapy.

It is difficult to find the combination of relevant expertise and experience, given the rarity of ocular melanoma, in an individual who is willing and available to serve on the committee. There are very few recognized thought-leaders in this area, owing to the rarity of the disease. Because there are so few oncologists who see a sufficient volume of patients to focus their practice on ocular melanoma, these experts will also have significant involvement in clinical trials in this area. To identify the appropriate experts for the panel, a search was conducted of literature in the field of ocular melanoma, including clinical trials, review articles, and internal documents on this subject. Other experts were considered, but were unable to participate due to financial conflicts deemed more substantial than the conflicts described in this waiver. The rarity of this disease, combined with the clinical trial involvement of the few existing experts, results in a unique challenge in identifying unconflicted participants. Dr. Sato is believed to be the least conflicted of the ocular melanoma experts considered, and is the only ocular melanoma expert attending this meeting.

Experts are needed to discuss whether this novel endpoint provides evidence of clinical benefit and whether the benefits observed outweigh the serious and life-threatening risks of this novel therapeutic approval. Without the input of physicians involved in the treatment and care of patients with ocular melanoma, the FDA division reviewing this product is concerned that they will lack the outside expertise necessary to make an informed decision on the pending new drug application for the Melblez Kit.

Further, in the interest of public health it is critical for the agency to have Dr. Sato review new products that can potentially provide treatment for ocular melanoma. Ocular melanoma is rare and the chance of survival in patients where the ocular melanoma has spread to the liver is poor. There are no approved treatments for ocular melanoma once it has metastasized. There will be an estimated 76,690 new cases of melanoma in the US in 2013; ocular melanoma (melanoma arising from the eye) accounts for approximately 2.5% of these new cases (2000 new cases) or an estimated 6 new cases per million people annually. Ocular melanoma differs from cutaneous melanoma in the pattern of metastatic spread and in driver mutations. The risk of metastatic disease is correlated with tumor size but may occur in up to 50% of patients with ocular melanoma and liver involvement is present in 90% of patients with metastatic ocular melanoma. Development of metastatic disease confers a very poor prognosis with reported median survivals of 4-5 months and one-year survival rates of 10-15%. In addition, the molecular pathways involved in the development of ocular and cutaneous melanoma are also different, e.g., approximately 50% of cutaneous melanoma has BRAF mutations while this is not reported in ocular melanoma. Therefore some treatment options available for patients with cutaneous melanoma (BRAF inhibitors) are not effective in treatment of patients with ocular melanoma. In contrast to metastatic cutaneous melanoma, and based on the specific metastatic pattern for ocular melanoma, the use of liver-directed

therapy is more common and constitutes an alternative treatment option for patients with metastatic ocular melanoma.

In summary, Dr. Sato is eminently qualified to serve on the Oncologic Drugs Advisory Committee for this specific issue. His experience and special knowledge make him essential to the Committee's discussions of this novel product.

Accordingly, we recommend that you grant a waiver for Takami Sato, M.D., Ph.D. a temporary voting member for the Oncologic Drugs Advisory Committee, 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):

Denied – The individual may not participate.

/s/
Jill Hartzler Warner, J.D.
Associate Commissioner for Special
Medical Programs (Acting)

April 16, 2013
Date