



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

DATE: March 25, 2009

TO: Randall W. Lutter, Ph.D.
Deputy Commissioner for Policy
Food and Drug Administration

THROUGH: Vince Tolino 15/
Director, Ethics and Integrity Staff
Office of Management Programs
Office of Management

Michael F. Ortwerth, Ph.D. 15/
Director, Advisory Committee Oversight and Management Staff
Office of Policy, Planning, and Preparedness

FROM: Jayne E. Peterson 15/
Acting Director
Division of Advisory Committee and Consultant Management
Center for Drug Evaluation and Research

Name of Temporary Voting Member: Mark Kieran, M.D., Ph.D.

Committee: Oncologic Drugs Advisory Committee Meeting

Meeting date: March 31, 2009

Description of the Facts on Which the Waiver is Based:

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

Dr. Mark Kieran is Director, Pediatric Medical Neuro-Oncology, in the Department of Hematology/Oncology at the Dana-Farber Cancer Institute. The Dana-Farber Cancer Institute (DFCI) is a temporary participating member of the Pediatric Brain Tumor Consortium (PBTC). PBTC is a cooperative research group that receives federal funding from the National Cancer Institute's (NCI). Dr. Kieran is the Study Chair and site investigator for a study of a competing product to Avastin.

- Phase I trial studying the side effects and best dose of AZD2171 (Cediranib/Recentin), an investigational product, in treating pediatric patients with recurrent, progressive, or refractory primary central nervous system tumors (brain or spinal tumors). Children less than 21 years of age with glioblastoma multiforme may be eligible to participate. The study is sponsored by the Pediatric Brain Tumor Consortium and the National Cancer Institute. The magnitude of the financial interest is \$0 - 50,000. A portion of the funds goes towards salary support for Dr. Kieran. The salary support does not increase Dr. Kieran's salary. Rather, it offsets the time he devotes to this project. The study began August 24, 2006, and will end in 2009.

Description of the Particular Matter to Which the Waiver Applies:

March 31, 2009, Oncologic Drugs Advisory Committee meeting to discuss supplemental biologic license application (sBLA) 125085/169 of Avastin (bevacizumab), sponsored by Genentech, in collaboration with F. Hoffmann La Roche, proposed indication as single agent, for the treatment of previously treated glioblastoma multiforme.

Basis for Granting the Waiver:

It is unlikely that the outcome of the matter will affect the Pediatric Brain Tumor Consortium study of a competing product in pediatric patients with brain tumors. Brain tumors in children are distinctly different from adult brain tumors, so although Avastin may be an effective treatment for adults with recurrent glioblastoma multiforme, it doesn't mean it will be equally effective in children. Therefore, any decision on the supplemental application for Avastin is unlikely to affect the cooperative research group study.

Additionally, it is speculative to assume that the committee's recommendations and subsequent FDA action concerning Genentech's application will directly and predictably effect this NCI-funded cooperative group trial. It is unlikely that any action, short of a "clinical hold" determination, would cause this study to be suspended or terminated. The "terms and conditions" of NCI's cooperative group agreement define the responsibilities, relationships, and governance of the research to be conducted, as well as the circumstances under which the terms of the agreement may be modified or the terminated. Consequently, NCI cannot arbitrarily decide to modify the terms of the agreement based on the outcome of the matter before the committee. Likewise, since the clinical trials cooperative group funding is not typically linked to any particular study, NCI cannot increase or decrease funding for a specific trial based on the outcome of the matter.

Further, according to the review division, Dr. Kieran's participation is essential to this meeting because of his unique expertise. Dr. Mark Kieran serves as a Director, Pediatric Medical Neuro-Oncology at the Dana Farber Cancer Institute, Harvard Medical School, Boston, MA. He also serves as Associate Professor of Pediatrics at Harvard Medical School. Dr. Kiernan is a member of the Society for Neuro-Oncology, the American Society for Clinical Oncology, the American Society of Pediatric Hematology/Oncology, the International Society of Pediatric Oncology, the American Association for Cancer Research and the highly selective Society of Pediatric Research. Dr. Kieran has published over 75 peer reviewed articles in prestigious journals such as Science, the Proceedings of the National Academy of Sciences, Blood, Cancer Research, Pediatrics, Pediatric

Hematology/Oncology, Pediatric Blood and Cancer, the Journal of Neuro-oncology and the Journal of Clinical Oncology.

Various treatments may be used to treat a malignant brain tumor. The type and number of treatments given are dependent upon many factors, including the size and location of the tumor and its growth rate. Radiation therapy and chemotherapy are generally used as secondary treatment for tumors that cannot be cured through surgery alone. Dr. Kieran's expertise is in Neuro-oncology involving the use of chemotherapeutic agents in the treatment of central nervous system malignancies with a specialty in Pediatrics. Locating qualified individuals to serve on this advisory committee has been difficult, even after screening all committee members and numerous special Government employees (SGEs). It is difficult to locate individuals with this expertise who were available and without disqualifying financial interests. Ten individuals with expertise in Neuro-oncology were invited to this meeting. Of these ten, seven were not able to attend due to conflicts of interest, incomplete appointment papers, and schedule conflicts. Three individuals are able to attend the meeting with expertise in Neuro-oncology; Dr. Kieran requiring a waiver, one individual specializing in Radiation oncology, and one specializing in oncologic Neuro-surgery.

It is imperative that the committee have members with expertise in Neuro-oncology specializing in Radiation oncology, oncologic Neuro-surgery, and the use of chemotherapeutic agents in the treatment of central nervous system malignancies in order to have a thorough and meaningful discussion at the meeting. Dr. Kieran's expertise in the use of anti-angiogenic agents and chemotherapy for the treatment of patients with central nervous system malignancies is critical for consideration of this application which involves an anti-angiogenic agent. It has been extremely challenging to identify physicians with expertise in the use of chemotherapeutic agents for central nervous system malignancies, a highly specialized area of oncology. Dr. Kieran has unique insights on one of the two central questions being posed to the Committee, specifically the potential for the pharmacologic effects of the drug to confound the interpretation of radiologic imaging, through its effects on edema. General Medical oncologists or general Radiation oncologists who deal primarily with solid tumors typically do not treat patients with glioblastoma multiforme and would not provide the same level of expertise for this specific disease. As noted above, Dr. Kieran's expertise in the use of anti-angiogenic agents and chemotherapy in the treatment of this disease allows him to offer a perspective that would not be shared by any other member of the committee.

Dr. Kieran served as a consultant and presented at the Pediatric Oncology Subcommittee of the Oncology Drugs Advisory Committee on December 6, 2006 to discuss endpoints for trials for pediatric brain tumors. Due to his expertise in Neuro-Oncology and his previous attendance and presentation at the above mentioned advisory committee meeting, the division feels strongly that Dr. Kieran has the background and expertise to lead an appropriate and stimulating discussion during the meeting. His knowledge of Neuro-Oncology and angiogenesis will allow for a thorough discussion of the meeting topic.

As described above, we believe that the interest of the Government in Dr. Kieran's participation outweighs the concern that a reasonable person may question the integrity of the Agency's programs and operations.

Thus we are requesting a waiver for Mark Kieran, M.D., a temporary voting member of the Oncologic Drugs Advisory Committee, from the conflict of interest prohibitions of 18 U.S.C. §208(a).

Certification:

The individual may participate – The need for the Special Government Employee’s services outweighs the potential for a conflict of interest.

The individual may participate – The individual’s participation is necessary to afford the advisory committee essential expertise.

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/_____
Randall W. Lutter, Ph.D.
Deputy Commissioner for Policy

3/27/09
Date