



MEMORANDUM

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To: Members and Consultants, Pediatric and Oncologic Drugs Advisory Committees

SUBJECT: **Overview of the April 27, 2009 Joint Meeting of the Pediatric Advisory Committee (PAC) and Oncologic Drugs Advisory Committee (ODAC)**

Thank you for agreeing to participate in the upcoming Joint Meeting of the PAC and ODAC on April 27, 2009. The committees will meet to discuss the scientific and ethical issues involved in developing drug treatments for children with diffuse pontine gliomas (DPG). Among the issues to be considered are (1) the scientific issues involved in identifying appropriate drug targets to study for the treatment of these tumors and (2) the ethical issues involved in obtaining and using brain biopsy specimens to evaluate gene expression patterns in children with DPG. The development of standards for microarray and proteomics-based identification of biomarkers and the exploitation of this information to identify appropriate drug targets in cancer therapies are two of the topics included in the March 2006 FDA Critical Path Opportunities List. Currently, the prognosis for children suffering from a diffuse pontine glioma is dismal, with death usually occurring within one year of diagnosis. Since the early 1990s, the standard of care has been to make the diagnosis on a characteristic MRI scan appearance and to treat using radiation therapy, with limited results. Early phase trials of empirical chemotherapy have been unsuccessful in improving survival. In the absence of tumor biopsy material, it is not possible to take advantage of recent advances in molecular profiling to establish potential drug targets for future experimental interventions. Thus, among other issues, the question has arisen as to whether the scientific need for this information may justify the performance of stereotactic brain biopsies, with the associated risks, in children with diffuse pontine gliomas for research purposes only.

The background material for this meeting includes articles grouped into six different categories, as listed on the enclosed bibliography. To guide your reading, here is a brief summary of the articles.

The articles by Hargrave et al (2006) and Massimino et al (2008) provide a general background on the diagnosis and treatment of children with DPG, and the failure of clinical trials to date to improve survival [1, 2]. As the risks of performing a stereotactic brain biopsy must be taken into consideration, the article by Roujeau et al [3] reports their experience with this procedure. The question of performing brain biopsies in children with DPG was the subject of a recent issue of the British Journal of Neurosurgery, with an editorial commentary [4] and two responses [5, 6] to a proposal [7] that such biopsies be performed.

The development of targeted therapy in oncology has been widely discussed over the past several

years with the development of new investigational techniques in molecular profiling. The journal *Clinical Trials* recently published three invited commentaries [8-10] and two responses [11,12] on the topic. This series provides an overview of some of the strengths, weaknesses, and concerns in using this technology to design clinical trials. As the adequacy of the science to establish a drug target in pediatric DPG is an important consideration, the background packet includes two general reviews of microarray and other technology. Jayapal and Melendez (2006) provide an overview of DNA microarray technology for drug target identification [13]. Sleno and Emili (2008) include a discussion of other proteomic methods.[14] Finally, there are two articles that discuss in more technical detail some important issues in the design of microarray studies, including sample size considerations.[15-16]

The FDA relies heavily on the knowledge, judgment, experience, and wisdom of the members of its advisory committees to provide us with feedback and advice on how best to promote and protect the public health of the United States. We thank you for your participation in this important discussion of the scientific and ethical issues involved in advancing the prospects of developing drug treatments for children with diffuse pontine gliomas. We are looking forward to this important meeting.

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