FDA/AACR/ASCO
Public Workshop on Brain Tumor Clinical Trial Endpoints

January 20, 2006
Bethesda North Marriott Hotel and Conference Center
North Bethesda, Maryland

Background Information

History and Goals of Cancer Drug Approval Endpoints Project

The Public Workshop on Brain Tumor Clinical Trial Endpoints is one of a series of FDA workshops evaluating potential endpoints for cancer drug approvals in the most common tumor types. Previous workshops have considered general issues related to trial endpoints as well as endpoints in lung, colorectal, and prostate cancer and acute leukemia. Summaries and presentations from these earlier workshops are posted on FDA's Web site for the Project on Cancer Drug Approval Endpoints.

Issues highlighted at these workshops are subsequently discussed at meetings of the Oncology Drugs Advisory Committee (ODAC), the FDA's statutory advisory body on issues related to oncology drugs. Discussions both at the workshops and at ODAC will inform guidance that FDA is writing on clinical endpoints for cancer drug approvals.

The American Association for Cancer Research (AACR) is providing logistical support for this workshop in conjunction with the American Society of Clinical Oncology (ASCO).

Workshop Purpose

The purpose of the Public Workshop on Brain Tumor Clinical Trial Endpoints is to engage in a thorough discussion of the pros and cons of a variety of endpoints for trials intended to support the approval of new drugs to treat primary brain tumors. The goal is to work toward the establishment of a set of principles on current and future standards of efficacy for these drugs. The primary focus will be on endpoints that are ready for incorporation into clinical trials now or in the near future. Workshop participants may identify key issues and areas in which knowledge is limited and may recommend issues or questions for further study. However, ***it is not the workshop panel's task to make recommendations or arrive at definitive conclusions.*** By law, FDA may take advice only from its statutory advisory committees.

Workshop Scope

The workshop's scope is limited to primary brain tumors. It will cover both adult and pediatric primary brain tumors to the extent that issues such as endpoints and imaging modalities are similar in adult and pediatric patients. Topics specific to primary brain tumors in pediatric patients (e.g., growth and development, cognitive testing, late effects) will be the subject of a

future advisory meeting or workshop. Brain metastases of other tumor types will also be addressed in other forums.

Workshop Structure

The workshop will consist of formal presentations examining different types of clinical trial endpoints for primary brain tumor drug approvals, interspersed with panel discussion. During discussion periods, panelists will address specific questions posed by the FDA that focus on issues such as the accuracy, reproducibility, and clinical relevance of the various endpoints about which data have been presented.

Audience Participation

The workshop agenda will include several opportunities for members of the audience to make comments and ask questions of the panel. Members of the audience are asked not to interrupt speaker presentations or panel discussion but to hold their comments and questions until the designated audience question period.

Workshop Agenda

FDA Laws and Regulations – Rationale for Evidence of Effectiveness

FDA (Dr. Rock) will provide context for questions posed to the panel by reviewing regulatory terms and principles, as well as types of endpoints that have been used to approve cancer drugs, including agents currently approved for treatment of primary brain tumors.

Classification and Clinical Assessment of CNS Tumors

Dr. Fine will discuss the classification of primary brain tumors and the implications of classification for clinical trial design and implementation. The presentation will also address survival, the current gold standard for demonstrating clinical benefit in primary brain tumors; other clinically observable outcomes that are potentially useful; the practicality of implementing a neurological examination in a randomized trial; the extent to which neurological signs, symptoms, and examination results are clinically meaningful; and whether endpoints other than survival can or should be validated in the setting of a rapidly progressive disease such as a brain tumor.

Clinical Trial Endpoints for Approval

1. Imaging-Based Outcomes

Four experts on imaging will make brief presentations. Drs. Provenzale and Patronas will address the advantages and disadvantages of various imaging modalities, including magnetic resonance (MR), computed tomography (CT), and positron emission tomography (PET) scanning. They will also discuss the relative precision of these modalities in assessing clinically meaningful response or disease progression and the ability to standardize imaging techniques

across trial sites. The current reimbursement status of imaging methods is not relevant to this discussion.

Drs. Ballman and Lamborn will address response definition and progression-free survival as they pertain to primary brain cancer. Dr. Ballman will discuss different measures of response, comparing the performance of the one-dimensional Response Evaluation Criteria in Solid Tumors (RECIST) with that of the World Health Organization's two-dimensional criteria for measuring response. She will compare the performance of conventional measures with that of computer-calculated volume estimation. Additionally, Dr. Ballman will present on the relationship between the endpoints of progression-free survival at 6 months and overall survival at 12 months for Phase II trials.

Dr. Lamborn will review recent data that address whether progression or the absence of progression at a specific time predicts survival duration, whether the timing of the assessment of progression (3 months vs 6 months) affects the strength of the prediction, and whether objective response or progression is a stronger predictor of survival.

Panel discussion of the above endpoints will focus on the analytic validity of the instruments employed in measuring imaging-based outcomes, as well as on the clinical relevance of these endpoints. Please see the complete list of Questions to the Panel for further details.

2. Patient-Reported Outcomes

Dr. Meyers will discuss the extent to which relief of tumor-specific symptoms represents clinical benefit to the patient. Issues surrounding the measurement of tumor-specific symptoms and the incorporation of tumor-specific symptom assessment into clinical trials will also be addressed.

Panel discussion of patient-reported outcomes will address the analytic validity of the instruments used, as well as their clinical relevance. Please see the complete list of Questions to the Panel for further details.

3. Workshop Summary

Following conclusion of the endpoint-specific presentations and panel discussions, Dr. Friedman will provide a brief summary of key points made at the workshop, focusing on three fundamental questions:

- Can a unified set of outcome assessments be applied to primary brain tumors as a group?
- How well do existing and imagined imaging techniques assess or predict clinical benefit?
- Might a unified PRO metric be validated to assess clinical benefit across both multiple therapeutic approaches and types of primary brain cancers?

4. Biomarker and Endpoint Research Priorities

Formal workshop proceedings will conclude at 4 p.m. The National Cancer Institute has invited panelists who are able to do so to stay for an optional one-hour discussion of research priorities for the further development and validation of the endpoints discussed throughout the day.