Questions to the Committee

Pediatric Oncology Subcommittee
of the
Oncologic Drugs Advisory Committee
December 6, 2006

Question 1.

- Brain tumors in children comprise a heterogeneous group of tumors whose biology, clinical manifestations, treatment and outcome differ from one another and from brain tumors in adults. Treatment decisions are in part based on risk-assignment models (*i.e.* low, intermediate and high-risk). For example, patients with low-risk characteristics receive therapy aimed at maintaining excellent survival while decreasing toxicity. Risk models may also be useful for regulatory purposes – e.g., in determining optimal endpoints and other study design features for new agents with the ultimate goal of market approval for the treatment of pediatric patients with brain tumors.

- A. Please discuss the value and/or pitfalls of categorizing pediatric brain tumors based on *risk strata,* as a first step to defining appropriate outcomes for use in regulatory decisions

- B. If it is appropriate to develop categories, please suggest: (a) categories and (b) criteria for such categories. The criteria could include, for example, histopathology characteristics and grade alone or in conjunction with other demographic and disease factors.

Question 2.

- FDA considers a variety of outcomes as informative for assessing efficacy for regulatory purposes. Examples of efficacy endpoints include overall survival, progression free survival, overall response rate and duration. For each of the risk strata (or specific tumor types) identified in your response to Q 1 please discuss study endpoints that represent a meaningful clinical benefit or a surrogate endpoint reasonably likely to predict clinical benefit. In your discussion consider:

- In what settings (population and design) is overall survival the appropriate endpoint for registration purposes?

- In what settings (population and design) can other endpoints (e.g., progression-free survival (PFS), overall response rate (ORR)) be considered?

- For PFS or ORR, what methodologies should be used to define the endpoint and to minimize potential bias?

Question 3.

- Neurological outcomes are important measures of response to as well as toxicity of treatment. Neurologic toxicity may manifest early and/or late in the course of treatment or follow-up, and ways to assess these outcomes, and their impact on the patient, will vary based on age of the patient, the functional status of the patient, validity and reproducibility of the assessment tools, etc. Please discuss:

- Acute effects (i.e. neuron-cognitive, memory loss)

- Late effects (cognitive – school performance, endocrine – thyroid, growth)

- Age and developmental status appropriate tools to identify/minimize effects of chemotherapy, radiation and surgical therapies on the developing brain and predictive models/markers for toxicity.

Question 4.

- New agents could be licensed on the basis that they demonstrate a reduction in toxicity without a decrement in efficacy (e.g., a drug designed to obviate the need for or to minimize doses of radiation). Such a claim usually necessitates evaluation in the context of a randomized, controlled non-inferiority study. However, such studies are particularly challenging when there is uncertainty regarding the active control effect size and when there are limited numbers of patients with the disease. Given the constraints of non-inferiority studies, please discuss in what clinical settings a non-inferiority study should be conducted in pediatric patients with brain tumors.