Pediatric Subcommittee
of the
Oncologic Drugs Advisory Committee

September 12, 2000

Questions to the Committee

The Pediatric Rule of 1998, based on the Pediatric Rule of 1994, states that if the course of a disease and the effect of a drug are similar in children and in adults, there is a Federal mandate to perform pediatric studies. It also states that a limited dataset can be used to register a drug for a pediatric indication.

The different tumor types seen in adults and children limit the application of the 1998 Pediatric Rule to pediatric oncology. The purpose of this meeting is to provide advice on when and how to apply the Pediatric Rule in pediatric oncology.

The method will be to

- describe the techniques used to diagnose and classify tumors
- discuss general principles that may apply to determine the relationship between tumor types
- apply the principles to specific examples
- discuss the types of clinical trial designs that may serve as paradigms or benchmarks when the conditions of the 1998 Pediatric Rule apply

The broad scope and complex nature of the topic may require several discussions to explore and clarify the issues, but in the interest of providing a framework for deliberation, questions on the major aspects are provided.

The session will begin with short presentations on the use of cytogenetics, histology, and microarrays to diagnose and classify tumors. There will be additional comments on special considerations for brain tumors and the interpretation of response to therapy. After the common ground has been established, the rest of the afternoon will be spent discussing the following questions. There may not be time to discuss all the questions, in which case another meeting, perhaps with some changes in the composition of the committee, will be scheduled.

Questions to the Committee

1) Consider the application of the following diagnostic criteria to the general problem of problem of describing similarities between adult and pediatric tumors. Recognizing the diversity of the various types of cancers, what criteria would you use to consider them similar and would you consider each condition as necessary or sufficient

a) if the same cytogenetic lesion is found in specimens from both tumor types?

b) if the histochemical pattern is the same?

c) if a molecular marker, such as overexpression of an oncogene, is the same?

d) How would you recommend microarray displays be utilized?
   i) Insufficient collective experience to make a recommendation
   ii) As supporting evidence along with other criteria
   iii) If the displays are within predefined tolerance sufficient evidence without confirmation by other techniques

The next two questions focus on the integration of cellular markers with clinical history.

2) Would you consider two tumor types to be the same or sufficiently similar if the diagnostic techniques met some consensus criteria based on cellular markers, but the anatomic locations differed in children and adults?

3) Would you consider two tumor types to be the same or sufficiently similar if the diagnostic techniques met some consensus criteria based on cellular markers, but the natural history with regard to growth rate or metastatic spreading differed in children and adults?

The next question focuses on specific tumor types.

4) What tumor types would you currently consider the same or sufficiently similar in adults and children? Note that not all possibilities are listed. The CNS tumors follow the WHO classification. Please state any restrictions or conditions with regard to age, anatomic location, or diagnostic features.
   a) Lymphomas
      i) Hodgkin's lymphoma
      ii) Non-Hodgkin's lymphoma
         (1) Small non-cleaved cell lymphoma
         (2) Other lymphomas
   b) Leukemias
      i) Acute myelogenous leukemia
         (1) Acute promyelocytic leukemia
         (2) Other FAB subtypes
      ii) Chronic leukemias
         (1) Philadelphia chromosome positive leukemia
         (2) Other types?
      iii) Lymphoid leukemia
         (1) Acute lymphoblastic leukemia
         (2) Non- ALL

c) Solid tumors
    i) Ewing's sarcoma and Ewing's-like tumors
    ii) Osteosarcoma
    iii) Rhabdomyosarcoma
    iv) Non-rhabdomyosarcoma connective tissue tumors
    v) Liver tumors
    vi) Germ cell tumors
    vii) Kidney tumors
    viii) Melanoma
    ix) Non-melanoma skin cancers
d) Central nervous system tumors
    i) Neuroectodermal tumors
    ii) Nerve sheath tumors
    iii) Meningeal tumors
    iv) Lymphomas
    v) Germ cell tumors
    vi) Germinomas
    vii) Cyst like lesions
    viii) Sellar tumors
        (1) Pituitary adenoma
        (2) Craniopharyngioma
e) Endocrine tumors
        (1) Thyroid carcinoma
        (2) Multiple endocrine neoplasias
        (3) Adrenal tumors other than neuroblastoma
f) Possible linkages with different histology
    i) Neuroblastoma and small cell lung cancer
g) Other suggestions?

Examining the benchmark for data collection

5) If two tumor types are considered the same or sufficiently similar and the efficacy and regimen are already established in adults
    a) would you recommend a therapeutic trial in children to confirm differences or similarities?
    b) If you recommend a confirmatory trial, what type of trial design would be most informative? What type of design would be considered adequate? Some possibilities include
        - a concurrent control parallel group design of adults and children sufficiently powered to calculate efficacy for each population
        - a single arm study with a sufficient number of patients to estimate a response rate within predefined confidence limits
        - a pilot study to determine dosing and safety with pharmacodynamic correlation to a clinical endpoint such as tumor response

    Please comment on any limitations with regard to tumor type, target population, sample size or trial design.

6) If a tumor type is considered the same or sufficiently similar in adults and children, and a new therapy is being developed (i.e. efficacy has not been established in any population), would you support a study design that included both adults and children in the eligibility criteria? Please comment on any limitations with regard to tumor type or target population.

    a) If you favor such a design, should efficacy results be pooled for analysis? Please comment on any limitations with regard to tumor type, target population, or trial design.