



## Memorandum

Date: November 13, 2006  
To: Pediatric Subcommittee of the Oncologic Drugs Advisory Committee Members, Consultants, and Guests  
From: Karen D. Weiss, M.D.  
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Subject: FDA Background Package for December 6, 2006 Meeting

Thank you for your willingness to participate in the subcommittee session scheduled for December 6, 2006. This one day meeting is devoted to a discussion on optimal clinical study endpoints for agents intended to treat brain tumors in pediatric patients. Our meeting follows an FDA/ASCO/AACR workshop entitled "Public Workshop on Brain Tumor Clinical Trial Endpoints" held in January 2006. That workshop did not specifically address unique issues relevant to pediatric patients with brain tumors such as tumor heterogeneity, biology and outcomes. Please see the link to the workshop summary included as part of background materials.

At this upcoming meeting, we hope to cover the following topics:

- Value of developing risk based categories for the purposes of broadly considering primary efficacy endpoints (given the heterogeneity of tumors)
- Patient and disease related factors to consider for such categorization
- Acceptable primary efficacy outcomes for regulatory decision, including use of radiographic and clinical measures and the timing of the assessments
- Study designs aimed at reducing toxicity while maintaining efficacy
- Aspects of neurological toxicity, including how and when to assess

Because you are all very familiar with the subject matter but possibly less familiar with regulatory issues, the background document is limited to these latter topics. In addition to the summary from the January 2006 workshop noted above, we also include an FDA draft guidance for Industry: "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" and selected power point slides and transcripts from a previous Pediatric Subcommittee held June 2001. The focus of the June 2001 subcommittee meeting was to identify the situations in which pediatric CNS

malignancies could be considered the same as adult malignancies for the purposes of applying the Pediatric Research Equity Act (PREA, formerly known as the Pediatric Rule). That focus is very different from our upcoming meeting.

Please contact me if you have questions. I look forward to an exciting and productive meeting with you on December 6.

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#### REFERENCES:

1. FDA Guidance for Industry: Clinical Trial Endpoints Guidance for the Approval of Cancer Drugs and Biologics (Draft). April 2005.
2. Meeting Summary: FDA/AACR Public Workshop on Clinical Trial End Points in Primary Brain Tumors. January 2006.
3. Pediatric Subcommittee of the Oncologic Drugs Advisory Committee Meeting. June 2001.
  - a. Slide Presentations
    - i. Henry S Friedman M.D., The Brain Tumor Center at Duke. "Challenges and Considerations in Linking Adult and Pediatric CNS Malignancies",:
    - ii. Susan M Staugaitis, MD PhD, Cleveland Clinic Foundation. "Perspectives on CNS Malignancies",
  - b. Meeting Transcript
    - i. Challenges and Considerations in Linking Adult and Pediatric CNS Malignancies - presentation and discussion; pg 28 (line 19) – pg 75 (line 14).
    - ii. Perspectives on CNS Malignancies – presentations and discussion; pg 213 (line 8) – pg 288.

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# Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

## *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER drugs) Grant Williams at 301-594-5758, (CDER biologics) Patricia Keegan at 301-827-5097, or (CBER biologics) Steven Hirschfeld at 301-827-6536.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**April 2005  
Clinical/Medical**

# Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

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# Guidance for Industry<sup>1</sup> Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

## I. INTRODUCTION

This guidance provides recommendations to sponsors on endpoints for cancer clinical trials submitted to the FDA to support effectiveness claims in new drug applications (NDAs), biologics license applications (BLAs), or supplemental applications.<sup>2</sup>

The FDA is developing guidance on oncology endpoints through a process that includes public workshops of oncology experts and discussions before the FDA's Oncologic Drugs Advisory Committee (ODAC).<sup>3</sup> This guidance is the first in a planned series of cancer endpoint guidances. It provides background information and discusses general regulatory principles. Each subsequent guidance document will focus on endpoints for specific cancer types (e.g., lung cancer, colon cancer) to support drug approval or labeling claims. The endpoints discussed in this guidance document are for drugs to treat patients with an existing cancer. This guidance does not address endpoints for drugs to prevent or decrease the incidence of cancer.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

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<sup>1</sup> This guidance has been prepared by the Division of Oncology Drug Products and the Division of Therapeutic Biologic Oncology Drug Products in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

<sup>2</sup> For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

<sup>3</sup> Transcripts are available at [http://www.fda.gov/cder/drug/cancer\\_endpoints/default.htm](http://www.fda.gov/cder/drug/cancer_endpoints/default.htm).

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37 cited. The use of the word *should* in Agency guidances means that something is suggested or  
38 recommended, but not required.

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## **II. BACKGROUND**

41  
42

43 Clinical trial endpoints serve different purposes. In conventional oncology drug development,  
44 early phase clinical trials evaluate safety and identify evidence of biological drug activity, such  
45 as tumor shrinkage. Endpoints for later phase efficacy studies evaluate whether a drug provides  
46 a clinical benefit such as prolongation of survival or an improvement in symptoms. The  
47 following sections discuss the general regulatory requirements for efficacy and how they have  
48 influenced endpoint selection for the approval of cancer drugs. Later sections describe these  
49 endpoints in more detail and discuss whether they might serve as measures of disease activity or  
50 clinical benefit in various clinical settings.

51

### **A. Regulatory Requirements for Effectiveness**

52  
53

54 The requirement that new drugs show effectiveness is based on a 1962 amendment to the Federal  
55 Food, Drug, and Cosmetic Act. This law requires substantial evidence of effectiveness and  
56 specifies that this evidence must be derived from adequate and well-controlled clinical  
57 investigations. Clinical benefits that have supported drug approval have included important  
58 clinical outcomes (e.g., increased survival, symptomatic improvement) but have also included  
59 effects on established surrogate endpoints (e.g., blood pressure or serum cholesterol).

60

61 In 1992, the accelerated approval regulations (21 CFR part 314, subpart H and 21 CFR part 601,  
62 subpart E) allowed use of additional endpoints for approval of drugs or biological products that  
63 are intended to treat serious or life-threatening diseases and that either demonstrate an  
64 improvement over available therapy or provide therapy where none exists. In this setting, the  
65 FDA may grant approval based on an effect on a surrogate endpoint that is *reasonably likely* to  
66 predict clinical benefit (“based on epidemiologic, therapeutic, pathophysiologic, or other  
67 evidence”). These surrogates are less well-established than surrogates in regular use, such as  
68 blood pressure or cholesterol for cardiovascular disease. A drug is approved under the  
69 accelerated approval regulations on condition that the manufacturer conduct clinical studies to  
70 verify and describe the actual clinical benefit. If the postmarketing studies fail to demonstrate  
71 clinical benefit or if the applicant does not demonstrate due diligence in conducting the required  
72 studies, the drug may be removed from the market under an expedited process. From December  
73 1992 to June 2004, 22 cancer drug applications were approved under the accelerated approval  
74 regulations. In the following discussion, we will use the term *regular approval* to designate the  
75 longstanding route of drug approval based on demonstrating clinical benefit to distinguish it  
76 from *accelerated approval* associated with use of a surrogate endpoint that is reasonably likely to  
77 predict benefit.

78

79 The nature of evidence to support drug approval, including the preferred number of clinical  
80 trials, is discussed in general FDA guidance documents. In most cases, the FDA has  
81 recommended at least two well-controlled clinical trials. In some cases, the FDA has found that  
82 evidence from a single trial was sufficient, but generally only in cases in which a single

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83 multicenter study provided highly reliable and statistically strong evidence of an important  
84 clinical benefit, such as an effect on survival, and in which confirmation of the result in a second  
85 trial would be practically or ethically impossible.<sup>4</sup> For drugs approved for treatment of patients  
86 with a specific stage of a particular malignancy, evidence from one trial may be sufficient to  
87 support an efficacy supplement for treatment of a different stage of the same cancer.<sup>5</sup>  
88

### **B. Endpoints Supporting Past Approvals in Oncology**

91 For regular approval, it is critical that the sponsor show direct evidence of clinical benefit or  
92 improvement in an established surrogate for clinical benefit. In oncology, survival is the gold  
93 standard for clinical benefit, but the FDA has accepted other endpoints for cancer drug approval.  
94 Indeed, in the 1970s the FDA usually approved cancer drugs based on objective response rate  
95 (ORR), determined by tumor assessments from radiologic tests or physical exam. In the early  
96 1980s, after discussion with the ODAC, the FDA determined that it would be more appropriate  
97 for cancer drug approval to be based on more direct evidence of clinical benefit, such as  
98 improvement in survival or in a patient's quality of life (QOL), improved physical functioning,  
99 or improved tumor-related symptoms — benefits not always predicted by ORR.

100  
101 Over the next decade, several endpoints were used as surrogates for benefit. Improvement in  
102 disease-free survival supported drug approval in selected surgical adjuvant settings (when a large  
103 proportion of patients had cancer symptoms at the time of recurrence). Durable complete  
104 response was considered an acceptable endpoint in testicular cancer and acute leukemia (a de  
105 facto improvement in survival because the untreated conditions were quickly lethal) and in some  
106 chronic leukemias and lymphomas (where it was clear that remission would lead to less  
107 infection, bleeding, and blood product support). The FDA has also considered that a very high  
108 ORR alone might sometimes support regular approval, but that response duration, relief of  
109 tumor-related symptoms, and drug toxicity should also be considered (O'Shaughnessy and  
110 Wittes et al., 1991, Commentary Concerning Demonstration of Safety and Efficacy of  
111 Investigational Anticancer Agents in Clinical Trials, *J Clin Oncol* 9:2225-2232). ORR has been  
112 an especially important endpoint for the less toxic drugs, such as the hormonal drugs for breast  
113 cancer, where improvement in this endpoint has been the basis for regular approval.  
114 Improvement in tumor-related symptoms in conjunction with an improved ORR and an adequate  
115 response duration supported approval in several clinical settings.

116  
117 In the last decade, in addition to its limited role in regular approval, ORR has been the primary  
118 surrogate endpoint used to support cancer drug accelerated approval for several reasons. First,  
119 ORR is directly attributable to drug effect (tumors rarely shrink spontaneously and, therefore,  
120 ORR can be accurately assessed in single-arm studies). Second, tumor response is widely  
121 accepted as relevant by oncologists and has a long-accepted role in guiding cancer treatment.  
122 Finally, if the ORR is high enough and the responses are of sufficient duration, ORR does indeed  
123 seem *reasonably likely* to predict clinical benefit.

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<sup>4</sup> See guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (<http://www.fda.gov/cder/guidance/index.htm>)

<sup>5</sup> See guidance for industry *FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products* (<http://www.fda.gov/cder/guidance/index.htm>)

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124  
125 Drugs approved under accelerated approval regulations must provide a benefit over available  
126 therapy. To satisfy this requirement, many sponsors have designed single-arm studies in patients  
127 with refractory tumors where, by definition, no available therapy exists.  
128

129  
130 **III. GENERAL ENDPOINT CONSIDERATIONS**  
131

132 The following is an overview of general issues in cancer drug development. A discussion of  
133 commonly used cancer endpoints is followed by a discussion of pertinent issues in cancer  
134 clinical trial design using these endpoints. Future guidance documents will discuss these issues  
135 in more detail with regard to specific treatment indications. Endpoints that will be discussed  
136 include overall survival, endpoints based on tumor assessments (e.g., disease-free survival, ORR,  
137 time to progression, progression-free survival, time to treatment failure), and endpoints based on  
138 symptom assessment. A comparison of important endpoints in cancer drug approval is provided  
139 in Table 1. Many of the issues relating to the proper analysis of efficacy endpoints are addressed  
140 in general FDA guidance documents.<sup>6</sup> Issues that commonly arise in oncology applications are  
141 discussed in this guidance.  
142

143 **Table 1. A Comparison of Important Cancer Approval Endpoints**

<b>Endpoint</b>	<b>Regulatory Nature of Evidence</b>	<b>Assessment</b>	<b>Some Advantages</b>	<b>Some Disadvantages</b>
Overall Survival	Clinical benefit	<ul style="list-style-type: none"><li>• Randomized studies needed</li><li>• Blinding not essential</li></ul>	<ul style="list-style-type: none"><li>• Universally accepted direct measure of benefit</li><li>• Easily measured</li><li>• Precisely measured</li></ul>	<ul style="list-style-type: none"><li>• Requires larger studies</li><li>• Requires longer studies</li><li>• Potentially affected by crossover therapy</li><li>• Does not capture symptom benefit</li><li>• Includes noncancer deaths</li></ul>
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"><li>• Randomized studies needed</li><li>• Blinding preferred</li></ul>	<ul style="list-style-type: none"><li>• Considered to be clinical benefit by some</li><li>• Needs fewer patients and shorter studies than survival</li></ul>	<ul style="list-style-type: none"><li>• Not a validated survival surrogate in most settings</li><li>• Not precisely measured; subject to assessment bias</li><li>• Various definitions exist</li></ul>

144 \*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as  
145 effect size, effect duration, and benefits of other available therapy. See text for details.

*continued*

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<sup>6</sup> See ICH guidance for industry *E9 Statistical Principles for Clinical Trials* (<http://www.fda.gov/cder/guidance/index.htm>)

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148 *Table 1, continued*

Endpoint	Regulatory Nature of Evidence	Assessment	Some Advantages	Some Disadvantages
Objective Response Rate (ORR)	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> <li>• Single-arm or randomized studies can be used</li> <li>• Blinding preferred in comparative studies</li> </ul>	<ul style="list-style-type: none"> <li>• Can be assessed in single-arm studies</li> </ul>	<ul style="list-style-type: none"> <li>• Not a direct measure of benefit</li> <li>• Usually reflects drug activity in a minority of patients</li> <li>• Data are moderately complex compared to survival</li> </ul>
Complete Response (CR)	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> <li>• Single-arm or randomized studies can be used</li> <li>• Blinding preferred in comparative studies</li> </ul>	<ul style="list-style-type: none"> <li>• Durable CRs represent obvious benefit in some settings (see text)</li> <li>• Can be assessed in single-arm studies</li> </ul>	<ul style="list-style-type: none"> <li>• Few drugs produce high rates of CR</li> <li>• Data are moderately complex compared to survival</li> </ul>
Progression Free Survival (PFS)	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> <li>• Randomized studies needed</li> <li>• Blinding preferred</li> <li>• Blinded review recommended</li> </ul>	<ul style="list-style-type: none"> <li>• Activity measured in responding and stable tumors</li> <li>• Usually assessed prior to change in therapy</li> <li>• Less missing data than for symptom endpoints</li> <li>• Assessed earlier and in smaller studies compared with survival</li> </ul>	<ul style="list-style-type: none"> <li>• Various definitions exist</li> <li>• Not a direct measure of benefit</li> <li>• Not a validated survival surrogate</li> <li>• Not precisely measured compared with survival</li> <li>• Is subject to assessment bias</li> <li>• Frequent radiologic studies are needed</li> <li>• Data are voluminous and complex compared to survival</li> </ul>
Symptom Endpoints	Clinical benefit	<ul style="list-style-type: none"> <li>• Usually needs randomized blinded studies (unless endpoints have an objective component and effects are large — see text)</li> </ul>	<ul style="list-style-type: none"> <li>• Direct measure of benefit</li> </ul>	<ul style="list-style-type: none"> <li>• Blinding is often difficult in oncology trials</li> <li>• Missing data are common</li> <li>• Few instruments are validated for measuring cancer-specific symptoms</li> <li>• Data are voluminous and complex compared to survival</li> </ul>

\*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Abbreviations: complete response (CR); objective response rate (ORR); progression-free survival (PFS).

**A. Overall Survival**

Overall survival is defined as the time from randomization until death from any cause, and is measured in the intent to treat (ITT) population. Survival is the most reliable cancer endpoint, and when studies can be conducted to adequately assess it, it is usually the preferred endpoint. An improvement in survival is of unquestioned clinical benefit. The endpoint is precise and easy to measure, documented by the date of death. Bias is not a factor in endpoint measurement.

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161 Overall survival almost always needs to be evaluated in randomized controlled studies.  
162 Historically controlled data are seldom reliable for time-dependent endpoints such as overall  
163 survival unless treatment effects are extreme (e.g., acute leukemia, testicular cancer). Apparent  
164 differences in outcome between historical controls and current treatment groups can arise from  
165 differences other than drug treatment, including patient selection, improved imaging techniques  
166 (which can alter tumor staging and prognosis), or improved supportive care. Randomized  
167 studies minimize the effect of such differences by allowing a comparison of outcomes in patient  
168 groups where such factors should be similar. Demonstration of a statistically significant  
169 improvement in overall survival is usually considered to be clinically significant, and has often  
170 supported new drug approval.

171  
172 Criticisms of survival as an endpoint stem not from doubts about the worth of a proven survival  
173 benefit, but from difficulties in performing studies large enough or long enough to detect a  
174 survival improvement, difficulties in determining a drug's effect on survival because of the  
175 confounding effects of subsequent cancer therapy, or a concern that the drug may be effective in  
176 only a small fraction of those treated, making it difficult to see an effect on survival in the whole  
177 population.

178  
179 **B. Endpoints Based on Tumor Assessments**

180  
181 In this section we discuss several endpoints that are based on tumor assessments and are  
182 therefore unique to oncology. These endpoints include disease-free survival, objective response  
183 rate, time to progression, progression-free survival, and time to treatment failure. The data  
184 collection and analysis of all time-dependent endpoints is complex, particularly when the  
185 assessments are indirect and based on calculations and estimates as is the case for tumor  
186 measurements. The discussion of progression-free survival data collection and analysis is  
187 particularly complex and is supplemented by tables in Appendix 3 of this guidance.

188  
189 Selection of tumor-assessment endpoints for efficacy trials should include two judgments. First,  
190 will the endpoint support accelerated approval (is the endpoint a surrogate reasonably likely to  
191 predict clinical benefit and does the drug provide an advantage over available therapy) or regular  
192 approval (is it an established and/or validated surrogate for, or a direct measure of, clinical  
193 benefit)? Second, will the results be reliable, given the potential for uncertainty or bias in tumor  
194 endpoint assessments? Drug applications using studies that rely on tumor measurement based  
195 endpoints as sole evidence of efficacy should generally provide confirmatory evidence from a  
196 second trial. Both the precision and the clinical meaning of endpoints based on tumor  
197 assessments can vary in different cancer settings. For instance, response rate determinations in  
198 malignant mesothelioma and pancreatic cancer are often unreliable because of the difficulty in  
199 measuring these tumors with currently available imaging modalities.

200  
201 When the primary study endpoint for drug approval is based on tumor measurements (e.g.,  
202 progression-free survival or ORR), it is recommended that tumor endpoint assessments generally  
203 be verified by central reviewers blinded to study treatment (see Appendix 4), especially when the  
204 study itself cannot be blinded. Although the FDA will generally not ask that all tumor images be  
205 submitted with the marketing application, it may need to audit a sample of the scans to verify the

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206 central review process. In all cases, we recommend submitting primary electronic data  
207 documenting tumor measurements and assessments.<sup>7</sup> Additional details regarding data  
208 collection are listed in Appendix 1.

209

### 210 *1. Disease-Free Survival*

211

212 Disease-free survival (DFS) is usually defined as the time from randomization until recurrence of  
213 tumor or death from any cause. Although DFS can also be an important endpoint when a large  
214 percentage of patients achieve complete responses with chemotherapy, the most frequent use of  
215 this endpoint is in the adjuvant setting after definitive surgery or radiotherapy. In either of these  
216 settings, DFS has special meaning to patients because until a recurrence occurs, a patient can  
217 hope for cure. Whereas overall survival is the standard endpoint for most adjuvant settings, DFS  
218 has been the primary basis of approval for hormonal therapy after initial surgery for breast  
219 cancer. An important consideration is whether prolongation of DFS represents intrinsic benefit  
220 or only a potential surrogate for survival prolongation. In December 2003, the consensus of the  
221 ODAC was that prolongation of DFS represented clinical benefit, but that the magnitude of this  
222 benefit should be carefully weighed against the toxicity of adjuvant treatment, particularly as  
223 measured by effects on patient function. In May 2004, the ODAC recommended that DFS be  
224 considered an acceptable endpoint for colon cancer drugs in the surgical adjuvant setting,  
225 provided certain conditions were met.<sup>8</sup> Additional cancer-specific guidances will address the  
226 acceptability of DFS in other cancer settings.

227

228 Important considerations in evaluating DFS as a potential endpoint include the estimated size of  
229 the treatment effect, proven benefits of standard therapies, and details of trial design. For  
230 instance, when a new drug is compared to a control drug that is known to improve overall  
231 survival, an important consideration is whether the DFS of the new drug is superior to, or only  
232 noninferior to, the control. Clearly, proof of superiority with regard to a surrogate endpoint is  
233 more persuasive than a demonstration of noninferiority. Furthermore, relying on a conclusion of  
234 noninferiority based on a surrogate endpoint to support a conclusion of noninferiority with  
235 respect to the definitive endpoint is problematic. Another critical issue is whether the duration of  
236 study follow-up is adequate to evaluate the durability of the DFS benefit.

237

238 We suggest that the protocol carefully detail both the definition of DFS and the schedule for  
239 follow-up studies and visits. Unscheduled assessments can occur for many reasons (including  
240 tumor-related symptoms, drug toxicity, anxiety), and differences between study arms in the  
241 frequency or reason for unscheduled assessments is likely to introduce bias. This potential bias  
242 can be minimized by blinding patients and investigators to the treatment assignments if feasible.  
243 The potential effects of bias due to unscheduled assessments can be evaluated by comparing their  
244 frequency between treatment arms and by performing statistical analyses that assign events from  
245 unscheduled visits to the time of the next scheduled visit.

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<sup>7</sup> See guidance for industry *Cancer Drug and Biological Products — Clinical Data in Marketing Applications* (<http://www.fda.gov/cder/guidance/index.htm>)

<sup>8</sup> Transcripts are available at [http://www.fda.gov/cder/drug/cancer\\_endpoints/default.htm](http://www.fda.gov/cder/drug/cancer_endpoints/default.htm).

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247 Another issue in defining DFS is whether deaths occurring without prior documentation of tumor  
248 progression should be scored as DFS events (disease recurrences) or should be censored in the  
249 statistical analysis. All methods for statistical analysis of deaths have limitations. The approach  
250 that seems less prone to introducing bias is to consider all deaths as recurrences. Limitations of  
251 this approach are a potential decrease in statistical power of the study (by *diluting* the cancer-  
252 related events with deaths not related to cancer) and a potential to falsely prolong the DFS  
253 estimates in patients who die after a long unobserved period. The latter could introduce bias if  
254 the frequency of long-term follow-up visits is dissimilar on the study arms or if there is  
255 nonrandom dropout due to toxicity. Some analyses count cancer-related deaths as DFS events  
256 and censor noncancer deaths. This method has the potential for bias in the post hoc  
257 determination of the cause of death. Furthermore, any method that censors patients, whether at  
258 death or at the last visit, assumes that the censored patients have the same risk of recurrence as  
259 noncensored patients. This critical assumption needs close examination in any setting where  
260 deaths are to be censored. In settings where deaths due to causes other than cancer are common  
261 (e.g., studies of patients with early metastatic prostate cancer), censoring deaths can be  
262 appropriate.

### 2. *Objective Response Rate*

266 ORR is the proportion of patients with tumor shrinkage of a predefined amount lasting for a  
267 predefined minimum period of time. Response duration is usually measured from the time of  
268 initial response until documented tumor progression. The FDA has generally defined ORR as  
269 the sum of partial responses plus complete responses. When defined in this manner, ORR is a  
270 measure of drug antitumor activity even in a single-arm study. Some sponsors have proposed  
271 including stable disease as a component of ORR; however, evaluating drug effects based on the  
272 stable disease rate generally involves comparison to a randomized concurrent control. Also,  
273 stable disease incorporates components of time to progression or progression-free survival,  
274 which can be captured in a separate measurement. A variety of response criteria have been  
275 considered appropriate, including the RECIST criteria (Therasse and Arbuck et al., 2000, New  
276 Guidelines to Evaluate Response to Treatment in Solid Tumors, J Natl Cancer Inst, 92:205-16).  
277 Important issues for determining the clinical and regulatory significance of ORR include  
278 response duration, the percentage of complete responses, the toxicity of treatment, and associated  
279 improvement in tumor-related symptoms. These issues, in addition to an assessment of benefits  
280 of existing therapies, determine whether ORR will support marketing authorization, either for  
281 regular approval (as a full surrogate for clinical benefit) or for accelerated approval (as a  
282 *reasonably likely surrogate*).

284 It is important that criteria for response and progression be detailed in the protocol, and data  
285 should be carefully and completely collected at intervals specified in the protocol.

### 3. *Time to Progression and Progression-Free Survival*

289 In the past, time to progression (TTP) (the time from randomization until objective tumor  
290 progression) and progression-free survival (PFS) (the time from randomization until objective  
291 tumor progression or death) have seldom served as primary endpoints for drug approval. Time  
292 to symptomatic progression, which would represent a clear clinical benefit, is infrequently

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293 assessed but would be a credible endpoint of a well-conducted (generally blinded) trial. In  
294 December 2003, the ODAC discussed both potential roles of TTP and PFS in cancer drug  
295 approval and the committee's preference for PFS versus TTP.<sup>9</sup> The ODAC suggested relying on  
296 these endpoints in selected clinical situations, such as diseases with low complete response rates  
297 or when documentation of a survival benefit in clinical trials can be difficult. In settings where  
298 most patients are symptomatic, the ODAC preferred measuring tumor response and symptom  
299 benefit. The definition of tumor progression varies widely; therefore, it is important that it be  
300 carefully detailed in the protocol.

301

### a. TTP vs. PFS

303

304 The ODAC consensus was that PFS is a better predictor of clinical benefit than TTP and thus  
305 preferable as a drug approval endpoint when used as a surrogate for clinical benefit (rather than  
306 just as an indicator of antitumor activity) because PFS includes deaths. Unanticipated effects of  
307 drugs on survival would thus be included in the endpoint. In the analysis of TTP, deaths are  
308 censored, either at the time of death or at an earlier visit. This approach is questionable because  
309 it can represent *informative censoring* (i.e., there may be a nonrandom pattern of loss from the  
310 study). It seems unlikely in most cancer settings that patient deaths are randomly related to  
311 tumor progression (e.g., it is likely that some deaths result from complications of undocumented  
312 cancer progression). Therefore, in most settings PFS is the preferred regulatory endpoint. In  
313 settings where most deaths are due to causes other than cancer, however, TTP can be an  
314 appropriate endpoint.

315

### b. PFS as an endpoint to support drug approval

316

317  
318 Some advantages and disadvantages of using PFS as an endpoint to support cancer drug approval  
319 are listed in Table 1. Conceptually, PFS has desirable qualities of a surrogate endpoint because it  
320 reflects tumor growth (a phenomenon likely to be on the causal pathway for cancer-associated  
321 morbidity and death), can be assessed prior to demonstration of a survival benefit, and is not  
322 subject to the potential confounding impact of subsequent therapy (unless worsening of a blood  
323 marker leads to a change in treatment prior to progression). Moreover, an effect on PFS occurs  
324 earlier than an effect on survival, so that a given advantage, say a median improvement of 3  
325 months, represents a larger (and thus more detectable) hazard ratio improvement than would a 3-  
326 month median survival benefit occurring later. The formal validation of PFS as a surrogate for  
327 survival for the many different malignancies that exist, however, would be difficult. Data are  
328 usually insufficient to allow a robust evaluation of the correlation between effects on survival  
329 and PFS. Oncology trials are often small, and proven survival benefits of existing drugs are  
330 generally modest. The role of PFS as an endpoint to support licensing approval varies in  
331 different cancer settings. In some settings PFS prolongation might be an accepted surrogate  
332 endpoint for clinical benefit to support regular approval, and in others it may be a surrogate  
333 reasonably likely to predict benefit for accelerated approval. Important considerations will be  
334 the magnitude of the effect, the toxicity profile of the treatment, and the clinical benefits and  
335 toxicities of available therapies. These issues will be discussed in future guidance documents for  
336 specific cancer settings.

337

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<sup>9</sup> Transcripts are available at [http://www.fda.gov/cder/drug/cancer\\_endpoints/default.htm](http://www.fda.gov/cder/drug/cancer_endpoints/default.htm).

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### 338 c. PFS trial design issues

339  
340 It is important that methodology for assessing, measuring, and analyzing PFS be detailed in the  
341 protocol and statistical analysis plan. It is also important to carefully define tumor progression  
342 criteria in the protocol. There are no standard regulatory criteria for defining progression.  
343 Sponsors have used a variety of different criteria, including the RECIST criteria. The broad  
344 outline presented in most published PFS criteria should be supplemented with additional details  
345 in the protocol and statistical analysis plan. It is important that visits and radiological  
346 assessments be symmetric on the two study arms to prevent systematic bias. When possible,  
347 studies should be blinded. Blinding is particularly important when patient or investigator  
348 assessments are included as components of the progression endpoint. It is important that the  
349 FDA and the sponsor agree prospectively on the protocol, data to be recorded on the case report  
350 form, statistical analysis plan (including analysis of missing data and censoring methods), and, if  
351 applicable, the operating procedures of an independent endpoint review committee (discussed in  
352 Appendix 4). The effect of follow-up visit frequency has been debated. Frequent regular  
353 assessments, depending on the type and stage of cancer, ensure that most progression events will  
354 be detected on radiologic scans rather than as symptomatic events. This approach increases the  
355 expense and difficulty of the study, including an increased data collection burden on the  
356 investigator and an increased number of scans for patients, and may not mirror clinical practice  
357 standards.

### 358 359 d. Analysis of PFS

360  
361 The analysis of PFS is complicated by missing data. It is important that the protocol specify  
362 what constitutes an adequate assessment visit for each patient (i.e., a visit when all scheduled  
363 tumor assessments have been done). The analysis plan should outline a comparison of the  
364 adequacy of follow-up in each treatment arm and specify how incomplete or missing follow-up  
365 visits will be handled with regard to censoring. For instance, if one or more assessment visits are  
366 missed just prior to the progression event, to what date should the progression event be assigned?  
367 It is important that the analysis plan specify the primary analysis and one or more sensitivity  
368 analyses. For instance, in the previous example, the primary analysis might assign the actual  
369 date of observed progression as the progression date. The sensitivity analysis might censor the  
370 data at the last adequate assessment visit. Although both analyses are problematic (the best  
371 solution to missing data is to have none), the conclusion is probably valid if it is supported by the  
372 results of both the primary and the sensitivity analyses. Other methods could be considered if  
373 adequately supported by the sponsor. The analysis plan should evaluate the number of deaths in  
374 patients who have been lost to follow-up for more than a substantial (prespecified) time. An  
375 imbalance in such deaths could bias the measurement of PFS, artificially prolonging PFS on the  
376 arm with less adequate follow-up.

377  
378 Because progression data can be collected from a variety of sources (including physical exams at  
379 unscheduled visits and radiologic scans of various types) and at a variety of times, it is important  
380 that data collection efforts for each assessment visit be limited to a specified short time interval  
381 prior to the visit. When data are collected over a longer time, the question then arises: What  
382 date should serve as the progression date or the censoring date? A common method is to assign  
383 progression to the earliest observed time when an observation shows progression and to censor at

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384 the date when the last radiologic assessment determined a lack of progression. Because this  
385 method could introduce an assessment bias, especially in unblinded trials, we recommend  
386 assigning the progression and censoring times to the time of the scheduled assessment visits. A  
387 study of time to symptomatic progression, if conducted blindly and with few scheduled  
388 assessments, in contrast, could use the actual time of observed symptom progression. The PFS  
389 date based on a death, however, would be the date of death rather than the assigned visit date  
390 since death ascertainment is not related to visit time and not subject to interpretation.

391  
392 Appendix 3 provides a set of tables for potential analyses of PFS that could be used for primary  
393 or sensitivity analyses. We recommend that plans for PFS data collection and analysis be  
394 discussed with the FDA at end-of-phase 2 meetings and verified in special protocol assessments.

### e. Future methods for assessing progression

397  
398 In the future, it is important that other methods of progression assessment be evaluated as  
399 potential surrogate endpoints for regular approval or accelerated approval. One proposed  
400 method (not used to date) is the single time point assessment which could decrease the  
401 complexity of progression assessment and eliminate time-dependent assessment bias. In the  
402 single time point analysis, progression would be assessed at baseline and at one prespecified time  
403 after randomization. If patients progress prior to the specified time, radiologic scans could  
404 document progression and the patient could go off-study. All other patients would have a  
405 detailed radiologic evaluation at the prespecified follow-up time. The statistical analysis could  
406 compare the proportions of patients on each study arm with progression on or before the  
407 prespecified time after randomization. Potential problems with this approach are decreased  
408 statistical power, potential for missing a small benefit at a time different from the prespecified  
409 time, and lack of information regarding the relationship between the single time point analysis  
410 and the familiar endpoints of progression-free survival and overall survival. Although this  
411 approach could provide some advantages and decrease assessment bias, study dropouts prior to  
412 progression could present the same difficulty as they do for all progression endpoints. Settings  
413 in which further evaluation of this approach seems warranted are those where a significant and  
414 durable effect on progression-free survival is expected and where complete progression-free  
415 survival data collection seems impossible or impractical.

### 4. *Time to Treatment Failure*

416  
417  
418  
419 Time to treatment failure (TTF) is a composite endpoint measuring time from randomization to  
420 discontinuation of treatment for any reason (including progression of disease, treatment toxicity,  
421 and death). Defined that way, TTF is not recommended as an endpoint for drug approval  
422 because it combines efficacy and toxicity measures. For example, suppose the standard  
423 comparator (Drug A) provides a known survival benefit, but only at the cost of considerable  
424 toxicity with many patients leaving therapy because of that toxicity. A nontoxic investigational  
425 drug (Drug B) could have a significantly longer TTF than Drug A solely because it caused fewer  
426 toxic dropouts. These data alone could not support drug approval because they would not  
427 demonstrate that Drug B is effective. Drug approval would require a demonstration of Drug B  
428 efficacy, such as a survival improvement or other clinical benefit.

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**C. Endpoints Involving Symptom Assessment**

Symptomatic improvement has always been considered a clinical benefit, and many FDA cancer drug approvals have used patient symptom assessments and/or physical signs thought to represent symptomatic improvement (e.g., weight gain, decreased effusion) as the primary evidence of effectiveness. To date, broader measures of health-related quality of life (HRQL instruments) have not served this role. HRQL is discussed in a separate FDA draft guidance on patient-reported outcomes (PRO).<sup>10</sup> The FDA has relied on symptom scores, signs, and symptoms representing obvious benefit (e.g., decreased esophageal obstruction, fewer bone fractures, reduced size and number of skin lesions, physician actions [need for radiation therapy in response to painful bone metastases], physician assessments of performance status, and patient-reported assessments of symptom scales). Relying on such evidence of clinical benefit as the basis for approval has allowed the FDA to approve cancer drugs earlier than if demonstration of a survival benefit had been required. It seems self-evident that cancer patients will be in most cases the best source for determining effects on patient symptoms, so that PRO instruments seem most appropriate. Formal PRO instruments can be designed that focus on specific symptoms (e.g., a pain scale) or on a broader array of physical, emotional, and activity measures.

The use of improvement of signs and symptoms or QOL assessments as primary endpoints to support cancer drug approval requires discrimination between tumor symptoms and drug toxicity, especially when evidence is based on comparison to a toxic active control. This poses particular problems for general HRQL scales, which, by definition, are multidimensional scales including elements other than physical problems. An apparent effectiveness advantage of one drug over another measured on a global HRQL instrument might simply indicate less toxicity of one product or regimen versus the other, a matter of interest but not an effectiveness measure. Morbidity endpoints used to date for cancer drug approvals have possessed *face validity* (value obvious to patients and physicians, for example, an endpoint based on functional measures such as the ability to swallow solids, liquids, or nothing) and have not measured benefit and toxicity on the same scale.

***1. Specific Symptom Endpoints***

One endpoint the FDA has suggested to sponsors is *time to progression of cancer symptoms*, an endpoint similar to time to progression. This endpoint would be a direct measure of clinical benefit rather than a potential surrogate. Sponsors have cited several problems with this approach. First, because few cancer trials are blinded, assessments can be biased and therefore unreliable. Another problem is the usual delay between tumor progression and the onset of cancer symptoms. Often alternative treatments are begun before reaching the symptom endpoint, which can confound the results. Many cancer trials are performed in patients with little prior exposure to chemotherapy and who usually have minimal cancer symptoms. Finally, it can sometimes be difficult to differentiate tumor symptoms from drug toxicity, a problem noted in

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<sup>10</sup> The draft guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims* is currently being developed and is expected to publish in the summer of 2005. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a CDER or CBER guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm> and the CBER Web page at <http://www.fda.gov/cber/guidance/index.htm>.

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471 discussions of time to treatment failure and HRQL. *Time to progression of symptoms* and *time to*  
472 *onset of symptoms* can be reasonable endpoints in cancer settings where treatment can be  
473 blinded, most progressing patients are symptomatic, no effective therapy exists, and less frequent  
474 radiologic follow-up is appropriate. Symptom data should be carefully collected using a  
475 validated instrument according to a schedule detailed in the protocol.

476  
477 A *composite symptom endpoint* can be appropriate when the benefit of a drug is multifaceted. It  
478 is important that the components of the endpoint be related and generally of similar clinical  
479 importance. Drugs have been approved for treatment of patients with cancer metastases to the  
480 skeleton based on a composite benefit endpoint consisting of one or more skeletal-related event  
481 (SRE) that would be anticipated to be associated with pain and other distress. SREs are defined  
482 as pathologic fractures, radiation therapy to bone, surgery to bone, and spinal cord compression.  
483 Clinical Benefit Response, a composite endpoint of pain and analgesic consumption reported by  
484 the patient, and performance status assessed by a physician, in part supported approval of a drug  
485 to treat pancreatic cancer.

486  
487 Selection of the appropriate population for study can be critical for documenting symptom  
488 benefit. Patients symptomatic at study baseline can be evaluated with a categorical symptom  
489 response analysis. This approach can be appropriate for diseases such as lung cancer, when most  
490 patients have symptoms at diagnosis. Studies of asymptomatic patients could use a time-to-first-  
491 symptom analysis. Even if the patient discontinues the study drug or begins a new drug,  
492 symptomatic progression could still be assessed if follow-up is continued until documentation of  
493 the first symptom. This approach is worth considering but has been infrequently attempted.

### 494 495 2. *Problems Encountered with Symptom Data*

496  
497 Many problems have been encountered in the analysis of symptom data submitted to the FDA.  
498 The most important problem in oncology is that few trials are blinded so that the possibility of  
499 observer bias is difficult to exclude. Missing data are common and often cast doubt on study  
500 conclusions. It is critically important to have frequent assessments to minimize long unobserved  
501 gaps. In addition, symptom severity should be addressed, rather than providing only a binary  
502 present or absent. Withdrawing treatment because of drug toxicity or tumor progression is one  
503 cause of missing symptom data. Ideally, when patients stop treatment, data collection forms  
504 should continue to gather information to inform the analysis. Symptom data could lead to a large  
505 number of different endpoints, and prospectively defined statistical plans need to correct for  
506 multiplicity if each symptom is treated as a separate endpoint.

### 507 508 **D. Biomarkers**

509  
510 To date, evidence from biomarkers assayed from blood or body fluids has not served as primary  
511 endpoints for cancer drug approval, although paraprotein levels measured in blood and urine  
512 have contributed to response endpoints for myeloma. Further research is needed to establish the  
513 validity of the available tests and determine whether improvements in such biomarkers are  
514 reasonably likely to predict clinical benefit (accelerated approval) or are established surrogates  
515 for clinical benefit (regular approval).

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517 Although tumor markers are not yet used alone as a basis for marketing approval, the FDA has  
518 sometimes accepted their inclusion as elements in composite endpoints. For instance, women  
519 with ovarian cancer often show clinical deterioration from progression of unmeasured tumor. In  
520 blinded randomized controlled trials in advanced refractory ovarian cancer, the FDA has  
521 accepted use of a composite endpoint that included CA-125. The occurrence of certain clinical  
522 events (a significant decrease in performance status, or bowel obstruction) coupled with marked  
523 increases in CA-125 was considered progression in these patients. The use of prostate specific  
524 antigen (PSA) was discussed at a recent workshop on prostate cancer endpoints. Different  
525 methods of evaluating PSA as an endpoint were discussed, including PSA response, PSA slope,  
526 and PSA velocity. Although the FDA has not yet accepted a PSA endpoint to support drug  
527 approval, evaluation of additional data and further discussions of PSA endpoints are planned in  
528 future workshops and ODAC meetings.<sup>11</sup>

529

530

### **IV. ENDPOINTS AND CLINICAL TRIAL DESIGN; SELECTED ISSUES**

532

533 By law, the FDA must base new drug approval decisions on substantial evidence of efficacy  
534 from “adequate and well-controlled investigations.” Regulations describe the meaning of  
535 “adequate and well-controlled investigations.” Studies must allow a valid comparison to a  
536 control and must provide a quantitative assessment of the drug’s effect. (See 21 CFR 314.126.)  
537 Below we discuss several issues related to the design of cancer trials intended to support drug  
538 approval.

539

#### **A. Single-Arm Studies**

541

542 The most reliable method for demonstrating efficacy is to show a statistically significant  
543 improvement in a clinically meaningful endpoint in blinded randomized controlled trials. Other  
544 approaches have also been successful in certain settings. In settings where there is no effective  
545 therapy and where major tumor regressions can be presumed to occur infrequently in the absence  
546 of treatment (a historical control), the FDA has sometimes accepted ORR and response duration  
547 observed in single-arm studies as substantial evidence supporting accelerated approval or even  
548 regular approval (e.g., when many complete responses were observed or when toxicity was  
549 minimal or modest). In contrast to the success of this approach, evidence from historically  
550 controlled trials attempting to show improvement in time-to-event endpoints such as survival,  
551 time to progression, or progression-free survival have seldom been persuasive support for drug  
552 approval, except when treatment provides survival outcomes that contrast markedly with  
553 historical experience (e.g., testicular cancer, acute leukemias). In most cases, however, these  
554 outcomes vary among study populations in ways that cannot always be predicted; for example,  
555 changes in concomitant supportive care or frequency and method of tumor assessment can differ  
556 by location or change over time. Consequently, comparisons involving these time-to-event  
557 endpoints generally need a concurrent control (preferably in a randomized trial), unless, as noted,  
558 the effect is very large.

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<sup>11</sup> Transcripts are available at [http://www.fda.gov/cder/drug/cancer\\_endpoints/default.htm](http://www.fda.gov/cder/drug/cancer_endpoints/default.htm).

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**B. Studies Designed to Demonstrate Noninferiority**

The goal of noninferiority (NI) trials is to demonstrate the effectiveness of a new drug showing that it is not less effective, by a predefined amount, than a standard regimen known to have the effect being investigated (Temple and Ellenberg, 2000, Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments, Part 1: Ethical and Scientific Issues, *Ann Intern Med*, 2000 Sep 19; 133(6):455-63).<sup>12</sup> The difference to be ruled out, the *noninferiority margin*, cannot be larger than the effect of the control drug in the new study. As that effect is not measured (the new study does not have a no-treatment arm), the effect must be assumed based on the previous studies of the control drug that documented its effect. If the new drug is inferior by more than the noninferiority margin, it would have no effect at all. In most cases the NI margin is not set at the control drug's full effect, but at some fraction of it (e.g., 50 percent), so that the study seeks to show that at least 50 percent of the control drug effect is preserved.

There are multiple difficulties with NI trials. NI trials rely on historical data to establish the expected size of treatment effect of the active control. In many situations adequate historical data for the control do not exist. Moreover, a critical assumption is that the treatment effect of the active control that was observed historically will also be observed in the current population in the new study. This assumption is difficult to support, as results of trials are almost never identical (although one can evaluate control regimen response rates in the historical and NI trial populations as some measure of comparability). Optimally, the estimated size of the treatment effect of the active control would be based on a comprehensive meta-analysis of historical studies that reproducibly demonstrate the effectiveness, compared to no treatment, of the control agent. In the oncology setting, however, information is often lacking on effects compared to a no-treatment control. The variability in the meta-analysis will be reflected in the choice of the noninferiority margin. But there may be little data from randomized controlled trials available to estimate the treatment effect and thus no basis for estimating the control treatment effect. Furthermore, subsequent events in the trial, especially crossover from the control, can invalidate NI survival analyses (producing a bias toward a showing of no difference). NI designs generally require many patients in order to provide meaningful results. Given the complex issues involved, we strongly recommend that sponsors designing noninferiority trials consult early with the FDA. Because of the difficulties with the design, conduct, and analysis of NI trials, a single NI trial seldom provides sufficient evidence of efficacy to support drug approval.

When the new treatment has a different toxicity profile from available treatments, it may be possible to *design around* the NI study problem by conducting an *add-on* study, adding new drug or placebo/no treatment to the standard therapy. This will not be possible if the goal is to show a new treatment to be less toxic than existing therapy (but still effective). In this case the NI design is unavoidable in order to demonstrate that the survival benefit of the standard drug is retained by the experimental drug. If the standard drug is associated with only a small proven survival benefit, however, interpretation of an NI study is difficult or impossible. Moreover, the size of such NI trials can be prohibitively large.

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<sup>12</sup> See ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (<http://www.fda.gov/cder/guidance/index.htm>)

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604           **C.     No Treatment or Placebo Control**

605  
606 Giving no anticancer drug treatment to patients in the control arm of a cancer study is often  
607 considered unethical, but, in some settings, it can be acceptable. For instance, in early stage  
608 cancer when standard practice is to give no treatment, comparison of a new agent to a no-  
609 treatment control would be acceptable. This approach would not be an ethical problem in the so-  
610 called *add-on* design, when all patients receive standard treatment plus either no additional  
611 treatment or the experimental drug. Using a control group that receives only best supportive care  
612 is acceptable in an advanced refractory setting where there is no effective therapy. Placebos  
613 (identical appearing inactive controls) are generally preferred to no-treatment controls because  
614 they permit blinding. With many cytotoxic cancer drugs, blinding may not be feasible because  
615 of a relatively high rate of recognizable toxicities, but newer interventions, many of them much  
616 less toxic, are increasingly being studied in blinded trials.

617  
618           **D.     Isolating Drug Effect in Combinations**

619  
620 Because marketing approval is usually for a single drug product rather than for a drug  
621 combination, clinical trials supporting regulatory approval need to isolate the effectiveness of the  
622 proposed agent. Evidence is needed showing not only the effectiveness of the regimen but also  
623 establishing the contribution of the new drug to that regimen. One way to demonstrate the  
624 individual contribution of a new drug in a regimen is using the *add-on* design previously  
625 discussed. Sometimes the clinical effects seen in early phases of development can be used to  
626 establish the contribution of a drug to a drug regimen, particularly if the combination is more  
627 effective than any of the individual components. We recommend discussing these issues with  
628 the FDA at end-of-phase 1 or end-of-phase 2 meetings.

629  
630           **E.     Trial Designs for Radiotherapy Protectants and Chemotherapy Protectants**

631  
632 Radiotherapy protectants and chemotherapy protectants are drugs designed to ameliorate the  
633 toxicities of radiotherapy or chemotherapy. Trials to evaluate these agents usually have two  
634 objectives. The first is to assess whether the protecting drug achieves its intended purpose of  
635 ameliorating the cancer treatment toxicity. Unless the mechanism of protection is clearly  
636 unrelated to the mechanism of antitumor activity (e.g., antiemetic agents which ameliorate  
637 nausea via central nervous system receptors), a second trial objective is to determine whether  
638 anticancer efficacy is compromised by the protectant. Because the comparison of antitumor  
639 activity between the two arms of the trial is a noninferiority comparison, a large number of  
640 patients may be required to achieve this objective. Generally, a second study is needed to  
641 confirm the findings. A critical question for the future is whether, in such cases where the same  
642 drug is studied in both arms, ORR should be considered a sufficient endpoint for comparing drug  
643 activity and benefit.

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646           **V.     SUMMARY AND CONCLUSION**

647  
648 Although general principles outlined in this guidance should help sponsors select endpoints for  
649 marketing applications, we recommend that sponsors meet with the FDA before submitting

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650 protocols intended to support NDA or BLA marketing applications. The FDA will ensure that  
651 these meetings include a multidisciplinary FDA team of oncologists, statisticians, clinical  
652 pharmacologists, and often external expert consultants. Sponsors may submit protocols after  
653 these meetings and request a special protocol assessment that provides the acceptability of  
654 endpoints and protocol design to support drug marketing applications.<sup>13</sup> Ultimately, of course,  
655 marketing approval will depend not only on the design of a single trial, but on FDA review of the  
656 results and data from all studies in the drug marketing application.  
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<sup>13</sup> See guidance for industry *Special Protocol Assessment* (<http://www.fda.gov/cder/guidance/index.htm>)

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**APPENDIX 1:**  
**THE COLLECTION OF TUMOR MEASUREMENT DATA<sup>14</sup>**

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The following are important considerations for tumor measurement data. The Agency recommends that:

- The case report form (CRF) and electronic data document the target lesions identified during the baseline visit prior to treatment. Retrospective identification of such lesions would rarely be considered reliable.
- Tumor lesions are assigned a unique identifying letter or number. This allows differentiating among multiple tumors occurring at one anatomic site and matching of tumors measured at baseline and tumors measured during follow-up.
- A mechanism ensures complete collection of data at critical times during follow-up. It is important that the CRF ensures that all target lesions are assessed at each follow-up visit and that all required follow-up tests are done with the same imaging/measuring method.
- The CRF contains data fields that indicate whether scans were performed at each visit.
- A zero is recorded when a lesion has completely resolved. Otherwise, disappearance of a lesion cannot be differentiated from a missing value.
- Follow-up tests allow timely detection of new lesions both at initial and new sites of disease. It is important that the occurrence of and location of new lesions be recorded in the CRF and the submitted electronic data.

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<sup>14</sup> *Tumor data* in this section refers to data in SAS transport files, not images. Images are not generally submitted to the NDA/BLA, but may be audited by the FDA during the review process.

**APPENDIX 2:**  
**ISSUES TO CONSIDER IN PFS ANALYSIS**

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The protocol and statistical analysis plan (SAP) of a study should detail the primary analysis of progression-free survival (PFS). This includes a detailed description of the endpoint, acceptable modalities for evaluating tumors, and procedures for minimizing bias when determining progression status, such as procedures for an independent endpoints review committee. It is important that one or two secondary analyses be specified to evaluate anticipated problems in trial conduct and to assess whether results are robust. The following are several important factors to consider.

- **Definition of progression date.** Survival analyses use the exact date of death. In analyses of PFS, however, the exact progression date is unknown. The following are two methods for defining the *recorded progression date (PDate)* used for PFS analysis.
  1. One approach assigns PDate to the first time at which progression can be declared:
    - For progression based on a new lesion, the PDate is the date of the first observation that detects the new lesion.
    - For progression based on the sum of target lesion measurements, PDate is the date of the last observation or radiologic assessment of target lesions (if multiple assessments are done at different times).This approach can introduce between-arm bias if radiologic assessments are done earlier or more frequently in one treatment arm.
  2. A second approach assigns the PDate to the date of the scheduled clinic visit immediately after all radiologic assessments (which collectively document progression) have been done. Although this approach provides a less accurate estimate of the true date of progression, the error should be symmetrically distributed between arms, and between-arm bias is minimized.
- **Definition of censoring date.** Censoring dates are defined in patients with no documented progression prior to data cutoff or dropout. In these patients, the censoring date is often defined as the last date on which progression status was adequately assessed. One acceptable approach uses the date of the last assessment performed. However, multiple radiologic tests can be evaluated in the determination of progression. A second acceptable approach uses the date of the clinic visit corresponding to these radiologic assessments.
- **Definition of an adequate PFS evaluation.** In patients with no evidence of progression, censoring for PFS often relies on the date of the last *adequate tumor assessment*. A careful definition of what constitutes an adequate tumor assessment includes adequacy of target lesion assessments and adequacy of radiologic tests both to evaluate nontarget lesions and to search for new lesions.
- **Analysis of partially missing tumor data.** Analysis plans should describe the method for calculating progression status when data are partially missing from *adequate tumor*

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

726 *assessment* visits. For instance, are the values for missing target lesions to be *carried*  
727 *forward*?

728

729 • **Completely missing tumor data.** Assessment visits where no data are collected are  
730 sometimes followed by death or by assessment visits showing progression; in other cases the  
731 subsequent assessment shows no progression. In the latter case, at first glance, it might seem  
732 acceptable to continue the patient on study and continue monitoring for evidence of  
733 progression. This approach, however, treats missing data differently depending upon  
734 subsequent events and could represent informative censoring. Therefore, another possibility  
735 is for the primary analysis to include data from subsequent PFS assessments when only a  
736 single follow-up visit is missed but censor data when there are two or more missed visits. It  
737 is important that the SAP detail primary and secondary PFS analyses to evaluate the potential  
738 effect of missing data. Reasons for dropouts should be incorporated into procedures for  
739 determining censoring and progression status. For instance, for the primary analysis, patients  
740 going off-study for undocumented clinical progression, change of cancer treatment, or  
741 decreasing performance status could be censored at the last adequate tumor assessment. The  
742 secondary sensitivity analysis would include these dropouts as progression events.

743

744 • **Progression of nonmeasurable disease.** When appropriate, progression criteria should be  
745 described for each assessment modality (e.g., CT scan, bone scan). It is important that scans  
746 documenting progression based on nonmeasurable disease be verified by a blinded review  
747 committee and be available for verification by the FDA if needed.

748

749 • **Suspicious lesions.** Sometimes new lesions are identified as suspicious. An algorithm  
750 should be provided for following up these lesions and for assignment of progression status at  
751 the time of analysis. For example, a radiological finding identified as suspicious at visit one  
752 might be verified as being a new tumor at visit three. It is important that the protocol or  
753 analytical plan clarify whether the progression time would be visit one or visit three.

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**APPENDIX 3:**  
**EXAMPLE TABLES FOR PFS ANALYSIS**

As discussed in Section III.B., sensitivity analyses may be helpful in determining whether the PFS analysis is robust. Different sensitivity analyses can be described in tables that specify how to assign dates of progression events and dates for censoring of progression data. The following three tables describe examples of three different sensitivity analyses:

- a. Table A represents a sensitivity analysis that only includes well-documented and verifiable progression events. Other data are censored. In Table A the progression dates are:
- Based only on radiologic assessments verified by an independent review committee (IRC). *Clinical progression* is not considered a progression endpoint.
  - Assigned to the first time when tumor progression was noted.
  - The date of death when the patient is closely followed. Deaths occurring after two or more missed visits, however, are censored at last visit.

**Table A. PFS 1 (includes documented progression only)**

<b>Situation</b>	<b>Date of Progression or Censoring</b>	<b>Outcome</b>
No baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: <ul style="list-style-type: none"> <li>• Date of radiologic assessment showing new lesion (if progression is based on new lesion); or</li> <li>• Date of last radiologic assessment of measured lesions (if progression is based on increase in sum of measured lesions)</li> </ul>	Progressed
No progression	Date of last radiologic assessment of measured lesions	Censored
Treatment discontinuation for undocumented progression	Date of last scan of measured lesions	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiologic assessment of measured lesions	Censored
New anticancer treatment started	Date of last radiologic assessment of measured lesions	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last radiologic assessment of measured lesions	Censored

***Contains Nonbinding Recommendations***  
*Draft — Not for Implementation*

776 The sensitivity analysis in Table B corrects for potential bias in follow-up schedules for  
 777 tumor assessment by assigning the dates for censoring and events only at scheduled visit  
 778 dates.  
 779

780 **Table B. PFS 2 (uniform progression and assessment dates)**

<b>Situation</b>	<b>Date of Progression or Censoring</b>	<b>Outcome</b>
No baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Date of next scheduled visit	Progressed
No progression	Date of last visit with adequate assessment	Censored
Treatment discontinuation for undocumented progression	Date of last visit with adequate assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate assessment	Censored
New anticancer treatment started	Date of last visit with adequate assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last visit with adequate assessment	Censored

781  
 782 **b.** The sensitivity analysis in Table C evaluates PFS according to the investigator's  
 783 assessment.  
 784

785 **Table C. PFS 3 (includes investigator claims)**

<b>Situation</b>	<b>Date of Progression or Censoring</b>	<b>Outcome</b>
No baseline assessment	Randomization	Censored
Progression documented between scheduled visits	Next scheduled visit	Progressed
No progression	Date of last visit with adequate assessment	Censored
Investigator claim of clinical progression	Scheduled visit (or next scheduled visit if between visits)	Progressed
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate assessment	Censored
New anticancer treatment started with no claim of progression	Date of last visit with adequate assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits or after patient misses one assessment visit	Date of death	Progressed
Death after an extended lost-to-follow-up time (two or more missed assessments)	Last visit with adequate assessment	Censored

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**APPENDIX 4:**  
**INDEPENDENT REVIEW OF TUMOR ENDPOINTS**

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791 Sponsors and the FDA need to be able to verify clinical trial results that support drug approval,  
792 including ORR and progression-free survival. ORR determined in single-arm studies can be  
793 verified by scrutiny of a limited number of images. However, when drug approval is based on  
794 measurement of progression-free survival in a randomized study, careful planning is needed to  
795 minimize bias and to allow the sponsor and the FDA to verify results. This is especially true  
796 when investigators and patients cannot be blinded to treatment assignment because of drug  
797 toxicities or manner of administration. An independent endpoints review committee (IRC)  
798 provides a mechanism to minimize bias in interpretation of the radiologic findings and  
799 independent adjudication of endpoints. We recommend that a clearly described written plan  
800 outlining the IRC function and process, sometimes called an independent review charter, be  
801 agreed upon with the FDA prior to study conduct. It is important that the plan describe how the  
802 independence of the committee will be assured; how images will be collected, stored,  
803 transported, and reviewed; how differences in image interpretation will be resolved; how clinical  
804 data will be used in final endpoint interpretation; and how, if needed, images and IRC results will  
805 be made available to the FDA for audit. The use of an IRC is discussed further in a draft  
806 guidance for the development of medical imaging products.<sup>15</sup>  
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<sup>15</sup> See draft guidance for industry *Developing Medical Imaging Drug and Biological Products, Part 3: Design, Analysis, and Interpretation of Clinical Studies*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a CBER guidance, check the CBER guidance Web page at <http://www.fda.gov/cber/guidelines.htm>.

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

January 20, 2006

Bethesda North Marriott Hotel and Conference Center  
North Bethesda, Maryland

**Meeting Summary**

**INTRODUCTION** (Dr. Richard Pazdur, FDA)

Dr. Pazdur welcomed everyone in attendance and noted that the purpose of the meeting was to have a wide-ranging discussion about the positive and negative aspects of various endpoints for trials intended to support the approval of new drugs to treat primary brain tumors. This workshop is the fifth in a series evaluating potential endpoints for drug approvals in the most common cancers. Previous workshops have considered endpoints in lung, colon, and prostate cancer and acute leukemia. 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.

The primary focus of the discussion should 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 and no votes will be taken. By law, FDA may take advice only from its statutory advisory committees.

Dr. Pazdur acknowledged that a tremendous need exists to develop new agents for the treatment of brain tumors, that many methodological hurdles need to be overcome in the validation of radiographic endpoints and patient-reported outcomes (PROs) for this type of tumor, and that clinical trial design issues also need to be addressed.

FDA has issued an overarching guidance document on endpoints for registration trials (*Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*; May 1998; available at <http://www.fda.gov/cder/guidance/1397fnl.pdf>) and intends to supplement this document with guidances focused on specific tumor types.

The final hour of the workshop will be chaired by representatives of the National Cancer Institute (NCI), who will lead a discussion aimed at identifying areas where further research is needed.

**REGULATORY BACKGROUND** (Dr. Edwin Rock, FDA)

Dr. Rock briefly reviewed the key pieces of legislation that established the framework for drug regulation in the United States: the Pure Food & Drug Act (1906); the Food, Drug, and Cosmetic Act (FDC, 1938); and the FDC Amendments (1962). The 1962 FDC Amendments for the first

time required sponsors, prior to marketing a new drug, to submit data documenting “substantial evidence of efficacy in adequate and well-controlled studies.”

In most cases, efficacy is considered equivalent to clinical benefit. FDA’s view of what constitutes clinical benefit has evolved over time. Currently, clinical benefit can be summarized as either longer life or better life; the latter is usually indicated by a direct measure of how the patient feels or functions. Clinical benefit can also be reflected by a surrogate that is not a direct measure of benefit.

In 1992 FDA introduced an alternative pathway to drug approval that is based on surrogates for clinical benefit. The accelerated approval (AA) mechanism was intended to speed medicines to market for serious or life-threatening diseases when an improvement can be shown over available therapy. A drug sponsor may apply for AA based on the demonstration of a favorable effect on a surrogate endpoint that is considered *reasonably likely to predict clinical benefit*. As a condition of approval, the sponsor must agree to provide additional data confirming clinical benefit, which may be generated either by another trial or by a distinct endpoint later in the same trial. Most AAs of cancer drugs have been granted on the basis of a demonstrated tumor response in a refractory setting, often supported by additional information.

For regular drug approval in oncology, survival is the undisputed “gold standard” for evidence of clinical benefit. During the 1990s, survival accounted for about one third of all cancer drug approvals. Demonstration of a favorable effect on how a patient feels or functions, measured by a valid, clinically relevant instrument, can also support regular approval. For example, mitoxantrone was approved for the treatment of hormone-refractory prostate cancer solely on the basis of pain relief, which was defined as a 2-point increase on a 6-point pain scale lasting at least 6 weeks.

Some surrogate endpoints have been accepted for regulatory purposes and may be used as the basis for regular drug approvals in oncology. For example, durable complete response is an accepted surrogate in acute leukemia; partial response is an accepted surrogate for approval of hormonal agents to treat metastatic breast cancer; and disease-free survival is an accepted surrogate for drug approvals in adjuvant breast cancer therapy.

### ***Strengths and Weaknesses of Accepted Oncology Endpoints***

**Survival.** The strength of survival as an endpoint is that it is unequivocal and easily measured. However, trials in which survival is the primary endpoint must be randomized, require a large sample size and lengthy follow-up, and are expensive. Another potential problem is that any beneficial effect of the experimental therapy may be “washed out” by crossover from the control arm to the experimental arm of the trial. This is usually more of a problem when the treatment effect is modest.

**Response rate.** Radiographic response rate is a surrogate endpoint that is unique to oncology. In the 1990s response rate was the basis for about half of regular approvals and almost all AAs. The strength of response rate as an endpoint is that tumor size reduction can be attributed in its entirety to therapy, whereas both survival and progression-free survival (PFS) are influenced to

some extent by the natural history of the disease. However, the response must be durable and the necessary duration of response is context-specific. It can be difficult to weigh the importance of a partial response vs. a complete response. In addition, response rate does not take into account stable disease, low-level responses that do not meet the criteria for partial response, or baseline disease burden.

Response rate can be effectively assessed for regulatory purposes in a single-arm trial. Acceptable criteria for response, stable disease, and progression must be defined prospectively. Response rate is more credible when supplemented by additional evidence of clinical benefit such as symptom improvement.

**Progression-free survival.** A strength of PFS as an endpoint is that the sample size and follow-up period are generally shorter than is necessary to show a survival benefit. Additionally, differences in PFS are not obscured by secondary therapy even if a crossover effect exists. Finally, PFS takes into account the potential toxic effects of therapy. However, because of the potential for bias in the interpretation of disease progression, trials in which PFS is a primary endpoint must be meticulously designed and executed and interpretation of progression must be blinded.

**Symptom palliation.** It is generally accepted that palliation of disease symptoms represents clinical benefit. About one fourth of drug approvals during the 1990s were based in part on symptom palliation. Symptom palliation is not synonymous with global measures of quality of life (QoL) ; the latter has not yet been accepted as the basis of any drug approval in the United States.

Symptom-palliation endpoints can be challenging to use. The development of symptom-palliation measurement instruments must be hypothesis-driven and validated. A measurement instrument's validity is easily compromised by trial design issues or by problems in execution. The credibility of symptom-palliation endpoints can be enhanced by blinding and by association with a biological effect of the drug such as response rate.

### ***Trial Design Considerations***

Randomized trials are invaluable for establishing the magnitude of a treatment effect and providing a thorough safety assessment. Blinding is essential whenever bias in measurement or interpretation could be an issue. Measurements must be clinically relevant with explicitly defined prospective analysis. For psychometric instruments and PROs, the concept underlying the instrument must be identified and mapped onto discrete elements of the measurements.

### ***Approvals of Drugs to Treat Primary Brain Tumors***

Several challenges have limited the development of effective new therapies to treat primary brain tumors, including the chemoresistance of brain tumors and problems with drug delivery to the central nervous system. Nonetheless, several drugs have been approved to treat this group of diseases:

- Nitrosoureas of DNA alkylating agents capable of crossing the blood-brain barrier after systemic administration
  - Orally administered lomustine (CeeNu), approved in 1976.
  - Intravenous carmustine (BiCNU), approved in 1977.
  - Both approvals based on tumor response rate (as were all drugs approved for cancer treatment prior to the 1980s).
  
- Carmustine wafer (Gliadel)
  - Synthetic biodegradable polymer impregnated with carmustine.
  - Approved in 1996 for treatment of recurrent glioblastoma multiforme (GBM) as an adjunct to surgery on the basis of a randomized, placebo-controlled trial in 222 glioma patients who progressed following surgery and radiation. Median survival for patients who received carmustine wafers was 7.4 months, vs. 5.5 months for those who received a placebo.
  - Approved in 2003 for initial treatment of high-grade malignant glioma as an adjunct to surgery and radiation. The basis of approval was a randomized, placebo-controlled trial in 240 patients with newly-diagnosed, high-grade glioma undergoing resection craniotomy. Median survival for patients who received carmustine wafers was 13.9 months vs. 11.6 months for those who received a placebo.
  
- Temozolomide (Temodar)
  - Orally available alkylating agent chemically related to dacarbazine.
  - Granted AA in 1999 on the basis of five durable complete responses among 54 patients with aplastic astrocytomas refractory to both nitrosoureas and procarbazine.
  - Granted regular approval in 2005 after confirmation of clinical benefit was obtained in a trial of 574 patients with newly diagnosed GBM. Patients were randomized following surgery to adjuvant radiation alone or radiation plus temozolomide followed by maintenance temozolomide for 6 months. Median survival was prolonged by 2.5 months in the temozolomide group.

### ***Charge to the Panel***

The panel was asked to discuss potential nonsurvival endpoints that may either directly represent clinical benefit or, as potential surrogates, be reasonably likely to predict clinical benefit in primary brain tumors. Questions that should be addressed included the following:

- Are the endpoints analytically valid and/or clinically relevant?
- Are the endpoints now or could they soon be useful, either individually or as composites, for establishing safety and efficacy, therefore supporting the drug approval process?

## **OVERVIEW: CLASSIFICATION AND TREATMENT OF PRIMARY BRAIN TUMORS; ISSUES AND EFFICACY ENDPOINTS IN GLIOMA CLINICAL TRIALS**

(Dr. Howard Fine, NCI)

Primary brain tumors are the leading cause of cancer-related deaths in children and the fourth leading cause of cancer-related deaths in people under the age of 54, Dr. Fine said. A significant increase in the incidence of brain tumors has been observed in people over the age of 60, although the extent to which this observation is an artifact of increased screening remains a matter of debate.

Brain tumors are of several different types, each with a distinct biology. Most of today's discussion will center on gliomas, the most common type of primary brain tumor. Other types of primary brain tumors include embryonal tumors (e.g., medulloblastomas), tumors of the lining of the brain (meningiomas) and tumors of the peripheral nerve cell sheath (e.g., schwannomas, neurofibromas). Brain metastases of systemic tumors present a different set of issues with regard to clinical trial design and will not be discussed today.

### ***Current Treatment Options for Gliomas***

Gliomas may be subdivided into benign (World Health Organization [WHO] grade I or "low grade") and malignant (WHO grades II to IV or "high grade") tumors. Radiographically complete surgical resection is generally considered optimal treatment for low-grade gliomas. Radiation therapy can halt disease progression for a time and probably increases survival; issues such as timing, dose, and volume of radiation therapy remain unresolved. The risk of long-term radiation-induced neurocognitive deficits is a significant concern as patients with low-grade gliomas generally live longer than those with malignant tumors. Interest is growing in the use of chemotherapy with agents such as temozolomide to delay radiation therapy. Radiographic responses are possible in patients with low-grade gliomas who receive chemotherapy, but no long-term outcome data are available.

For high-grade gliomas, complete surgical resection is generally considered optimal treatment, although only retrospective data support this. Radiation therapy remains the foundation of treatment. Long-term neurocognitive deficits are less of a concern than in low-grade tumors because patients usually do not live long enough to experience this toxicity.

Three meta-analyses have shown that post-radiation chemotherapy results in a small but statistically significant survival benefit. The definitive European Organization for Cancer Research and Treatment (EORTC) trial showed a benefit for temozolomide given either concurrently with radiation therapy or after radiation therapy to patients with GBM; median survival was increased by about 2.5 months and 2-year survival by about 18%. Two trials of carmustine wafers have shown small but statistically significant increases in survival in both recurrent and newly diagnosed GBM.

With no treatment, median survival from the time of diagnosis for patients with malignant gliomas is 3 months. Surgery may extend median survival to 4 or 5 months; adding radiation to surgery extends it to 10 months. Adding temozolomide chemotherapy to radiation and surgery has now extended median survival to 14 months. Existing therapies are clearly of limited effectiveness and new, more effective therapies are sorely needed.

### ***Obstacles to the Development of More Effective Glioma Therapies***

The central nervous system is a unique micro-environment. Because the brain is essential to survival, surgery cannot be performed with wide margins as is done in the resection of systemic tumors. The brain is physiologically different from other tissues and these physiologic differences have profound effects on both tumor biology and on drug delivery. The brain endothelium differs significantly from other endothelial tissue, resulting in the blood-brain barrier. The brain lacks a lymphatic system and is an immunological sanctuary, thus presenting a different set of challenges with regard to the use of immunologic therapies.

Central nervous system tumors differ biologically from systemic tumors. They generally have high drug resistance, both intrinsic and acquired. They are nonmetastatic in that they rarely spread to other organs, but they are highly infiltrative.

Brain tumors present specific pharmacologic challenges. In addition to the problem of the blood-brain barrier, it has become clear within the past decade that hepatic cytochrome P450 isoenzymes are intrinsic to the metabolism of most chemotherapy drugs. Many patients with brain tumors are taking anti-epileptic drugs that induce or inhibit the P450 system. Patients who are on enzyme-inducing anti-epileptic drugs (EIAEDs) have significantly altered drug metabolism. For example, for patients taking phenytoin (Dilantin) or carbamazepine (Tegretol), the maximal tolerated dose (MTD) of paclitaxel or CPT-11 may be 3- to 5-fold higher than for patients with systemic tumors. This has profound implications for clinical trials. It is necessary, for example, to conduct two Phase 1 studies to establish two different MTDs: one for patients who are taking EIAEDs and one for those who are not.

Patients with gliomas are very heterogeneous. Factors such as age, performance status, extent of resection, neurologic deficits, and use of glucocorticoids have significant effects on prognosis. Tumors are also heterogeneous; distinctions between tumor histologies are often unclear, resulting in inter-observer variability rates as high as 30% to 40%. Even tumors with similar histology can have very different genetic characteristics; for example, expression of the HMG1 enzyme contributes to resistance to temozolomide. Additionally, the anatomic location of a tumor (e.g., brain stem, thalamus, right frontal lobe) can significantly affect the outcome.

### ***Clinical Trial Design Issues***

All of the above issues present challenges to the design of clinical trials of therapies for primary brain tumors. Because gliomas are rare and it is difficult to accumulate sufficient numbers of patients for a clinical trial, clinical researchers have attempted to use historical data to make comparisons. Unfortunately, the literature is severely flawed. Investigator-selected criteria for response are variable and almost always include stable disease. Past trials have often not required

response duration and have not controlled for the effects of glucocorticoids, the type of magnetic resonance imaging (MRI) technology used to measure response, or for important prognostic factors such as tumor type, grade, age, and performance status.

NCI-sponsored brain tumor research consortia are now generating databases that will improve the objective nature of neuro-oncology trials, but these databases are not yet freely available. Moreover, they may be of limited utility because patients enrolled in trials conducted by NCI-sponsored consortia may represent average patients in the community. An additional challenge for the design of clinical trials is that, with the possible recent exception of radiation +/- temozolomide, no agreed-upon standard of care exists upon which to base comparisons.

### ***Clinically Meaningful Endpoints For Patients With Brain Tumors***

Survival is both an objective and clinically meaningful endpoint, but it requires large randomized studies in a relatively rare disease. Few adequate historical controls exist to allow non-randomized comparisons. Small patient numbers make it very difficult to study any glioma subtype except GBM. It is difficult to balance hugely important prognostic factors, particularly in the setting of recurrent brain tumors. Finally, survival is not an appropriate endpoint for studies of palliative drugs.

Disease-stabilization endpoints (e.g., PFS, time to progression) offer the advantage of requiring a shorter time to data maturation. Because tumor progression is usually associated with worsening neurological function, tumor stabilization might translate to improved QoL, but few data are available to support this. In a rapidly progressive disease such as GBM, however, progression tends to precede death by a few months at most, so it is unclear how much time is really saved by the use of progression rather than survival as an endpoint. Disease-stabilization endpoints have many of the same disadvantages as survival: the need for large randomized studies in a rare disease, inadequate historical controls for non-randomized comparisons, small patient numbers, and inappropriateness for studies of palliative drugs.

Clinical response is associated with patient symptoms, performance, and QoL. However, patient symptoms are highly subjective. Neurological signs are objective but are affected by significant inter-examiner variability. Symptoms are also affected by concomitant medications (e.g., glucocorticoids, antiepileptics, anticoagulants).

Radiographic response is somewhat objective and is the historical standard, but has many disadvantages. Because gliomas usually do not form “lumps” in the brain, MRI scans are often not looking at the tumor directly but rather at the tumor’s effects on normal brain architecture. Tumors cause several different signal abnormalities on MRI scans.

Gadolinium enhancement is measured as a response criterion in most clinical trials. However, gadolinium enhancement does not measure nonenhancing tumors. This approach tends to measure vascular permeability rather than tumor; factors such as radiation damage and use of glucocorticoids or vascular-stabilizing drugs can affect vascular permeability. No standard way of measuring gadolinium enhancement exists; the Response Evaluation Criteria in Solid Tumors (RECIST) have not been validated in brain tumors.

With regard to PRO and QoL endpoints, although treatments that improve patients' neurological functioning, increase their ability to live independently, and decrease seizures would be valuable, no clear methods currently exist for measuring these parameters.

### ***Conclusions***

In summary, few effective treatments exist for primary brain tumors. No systemic therapy is approved for recurrent GBM. The literature from which to derive historical control data is largely undependable. Evaluation of clinical trials is affected by patient and tumor heterogeneity, factors shown to have a greater impact than any given therapy on patient outcome. Survival is currently the only clearly accepted trial endpoint. Treatment that resulted in tumor and symptom stabilization would be considered clinically meaningful and useful, but how best to objectively measure such outcomes remains unclear.

Dr. Fine ended his presentation by posing two questions that he said he hoped the workshop would address:

- What therapeutic outcomes are truly clinically meaningful to patients with gliomas?
- What clinical trial endpoints are representative of those outcomes and how can they be objectively and reproducibly measured?

## **CLINICAL TRIAL ENDPOINTS FOR APPROVAL: IMAGING-BASED OUTCOMES**

### **Magnetic Resonance Imaging Surrogate Markers of Brain Tumor Therapeutic Response** (Dr. James Provenzale)

Dr. Provenzale began by saying that if he could sum up Dr. Fine's talk in three words, those words would be "validation," "quantification," and "reproducibility." Those words also describe the three issues that imaging scientists face in dealing with brain tumors, he said.

MRI is the imaging technique most commonly used to diagnose and assess therapeutic response in brain tumors. However, conventional MR imaging of brain tumors provides anatomic, but not physiologic, information. In most trials of brain tumor therapies, tumor assessment is based on both tumor size and enhancement characteristics.

The principal advantages of MRI compared with computed tomography (CT) imaging are that MRI makes it possible to image the tumor in multiple planes, offers better image resolution, and offers more advanced imaging techniques. However, MR imaging takes more time than CT scanning and cannot be performed on patients who have incompatible implanted devices such as aneurysm clips and cardiac pacemakers. Thirdly, it can be difficult to perform an adequate MRI scan on a very ill patient who has difficulty lying very still. It can also be difficult to monitor patients who are on respirators or are receiving continuously infused drugs.

CT scanning takes less time to perform than MRI and is useful for answering basic questions. Perfusion imaging can be performed with CT, but the role of this type of imaging in brain tumor

assessment is underexplored. However, the depiction of tumor extent is inferior with CT scanning compared with MRI. Like MRI, CT scanning provides very limited physiologic information.

Currently, brain tumors are assessed in clinical trials primarily by measuring them at the widest point of their diameter in accordance with the RECIST criteria. This provides no information about tumor physiology. At a time when many drugs can alter tumor physiology, new imaging techniques are needed that keep pace with these pharmacologic advances. Additionally, current imaging methods provide only a gross estimation of tumor aggressiveness. Three advanced MR techniques may be able to address these challenges.

- **MR spectroscopy** can be used to obtain metabolic profiles throughout the brain, which can be helpful in trying to determine what is happening in unenhancing areas of a tumor or in tissue adjacent to a tumor.
- **MR diffusion imaging** measures the rate of diffusion of water molecules throughout the brain in both tumor and normal tissue. The presence of tumor cells restricts the diffusion of water molecules in the brain; when the tumor responds to treatment, water molecules can diffuse more readily. Diffusion imaging can be used to measure therapy-induced changes in water mobility within the brain. Preliminary data suggest that this technique may be able to indicate within a few weeks whether or not the tumor is responding to therapy.
- **MR perfusion imaging** is a technique for monitoring the effectiveness of antiangiogenic therapy. Angiogenesis is the development of new blood vessels within tumors, which is essential for tumor growth beyond a few millimeters. Studies in animal models have shown that restricting angiogenesis severely impairs tumor growth. Angiogenic factors in tumors increase both the number and the permeability of blood vessels. High cerebral blood volume (CBV) can be an indicator of tumor aggressiveness. Perfusion imaging techniques can measure CBV and vessel permeability, both of which should decline in the presence of an antiangiogenic agent.

In summary, several advanced MR imaging techniques can provide both physiologic and anatomic information about brain tumors. These techniques, which are currently experimental, need to be used to measure tumor responses to therapy and to determine whether a tumor response correlates with outcome. Secondly, some of these techniques show promise as surrogate biomarkers. The jury is currently out on whether one technique is superior to any other.

### **Positron Emission Tomography Scanning with FDG in Brain Tumors; Brain Tumor Measurements in Assessing Response to Treatment** (Dr. Nicholas Patronas)

Experience over the past 25 years has shown that positron emission tomography (PET) scanning is valuable in assessing tumor growth, providing guidance for surgical biopsy, assessing malignant transformation, addressing the issue of recurrence vs. necrosis after radiation therapy, and evaluating the extent of tumor growth within the cranial cavity, Dr. Patronas said.

As yet, data are sparse on the value of using PET scanning to assess response to treatment. Response assessment may be measured qualitatively (i.e., visually or by means of a ratio of pathologic to normal tissue) or quantitatively (i.e., standardized uptake value [SUV]). Another approach to quantitative measurement, calculation of the rate of glucose utilization, is no longer used.

SUVs are used in a variety of tumor types to measure prognosis and disease progression or regression. However, there are greater challenges in the application of this measurement approach to brain tumors because, unlike many other organs, the brain is highly metabolically active. Factors influencing SUV measurements include the plasma glucose level, the injected dose of the isotope, the time after injection that the scan is performed, use of medications that affect glucose metabolism (e.g., steroids, insulin), partial volume effects, and body weight vs. lean body mass.

Factors influencing image quality and lesion conspicuity on MRI include the signal-to-noise ratio, contrast issues, and image resolution and homogeneity. Factors influencing tumor enhancement include the dose of the administered contrast agent, the compound used, the time delay prior to scanning, medication use, renal function, hemodynamic alterations, and partial volume artifacts (i.e., obliquity of brain sections). It is important to ensure that every time the tumor is measured by linear measurement technique, images are coregistered by date to ensure that the same “slice” is evaluated.

Measuring tumor diameter is probably an outdated methodology, as small percentage changes in diameter can reflect much larger changes in tumor volume. Both manual and automated segmentation techniques provide more accurate measurements of tumor volume than diameter measurement; these techniques have the further advantage of not being operator-dependent. Automated segmentation is more accessible now, is easy to perform, and does not require manual manipulation of the image. In the post-contrast MRI, each tissue type has a unique distribution of pixel intensities. In automated segmentation the intensity of distribution is estimated for cerebrospinal fluid, normal brain tissue, and enhancing tumor. Each pixel’s intensity is compared with these distributions and segmented according to its most probable tissue class.

### **Response and Progression-Free Survival Endpoints for Gliomas (Dr. Karla Ballman)**

Dr. Ballman presented analyses of data from the North Central Cancer Treatment Group (NCCTG) database. The first study compared the performance of, and the extent of agreement between, the unidimensional (1D) RECIST criteria, the WHO bidimensional (2D) criteria, and computer-calculated measurements of tumor area and volume. Tumors were classified at various time points as progressive disease, stable disease, or disease regression. All measurements were conducted in newly diagnosed gliomas of different tumor types and different grades. Patients with enhancing tumors generally were older and had higher-grade tumors; patients with non-enhancing tumors generally were younger and had lower-grade tumors.

Agreement among methods was moderate at best. Determination of response by the 1D and 2D criteria did not differ significantly. No evidence of an association between response and survival

was seen for enhancing/nonenhancing tumor measurements. Some evidence of an association between progression and survival was observed for enhancing tumor measurements. Small sample size may explain some of the lack of agreement. Other limitations are that the data are from a single group and the analysis was not done by tumor type and grade.

The second study examined the relationship between PFS at 6 months and overall survival (OS) at 12 months in Phase 2 GBM trials. The study purposes were to determine the relationship between the endpoints, determine whether the relationship was similar in trials of newly diagnosed GBM patients and trials of patients with recurrent GBM, and assess whether it is reasonable to use 6-month PFS in place of 12-month OS as an endpoint for Phase 2 GBM trials. Data were pooled for 1,359 patients in 12 trials, all of which were negative.

Patient-level agreement was moderate for trials of both newly diagnosed and recurrent disease. Trial-level agreement was mixed for both types of trials; correlation was moderate (less than 0.90) and agreement of study results was good (88-90%). PFS at 6 months was strongly associated with OS at 12 months. Once again, all data are from a single cooperative group and all are from negative trials. Importantly, this was not a formal surrogate endpoint analysis.

### **Is Progression-Free Survival a Clinically Relevant Endpoint for Clinical Trials Testing Treatments For Malignant Glioma at Time of Progression? Report of Data From the North American Brain Tumor Consortium (Dr. Kathleen Lamborn)**

Dr. Lamborn presented data from an analysis of 13 single-arm Phase 2 trials involving 611 patients with high-grade gliomas. The trials were performed at multiple institutions participating in the North American Brain Tumor Consortium (NABTC). Entry criteria were similar for all trials: patients were adults with Karnofsky Performance Status (KPS) scores of at least 60, proof of disease progression by imaging, adequate organ function, prior radiation therapy, and a limited number of prior chemotherapies. Evaluable or measurable disease was not required. The primary endpoint for all trials was 6-month PFS. The purpose of the analysis was to determine whether progression status at various time points predicted OS from those time points.

For patients with both Grade 3 and Grade 4 tumors, progression status strongly predicted survival from the time of assessment for each of the planned assessment times (9 weeks, 18 weeks, and 26 weeks) during the first 6 months from the start of the study, indicating that delay in time to progression predicts for improved patient survival. This finding is limited by the fact that the data were not derived from randomized trials and none of the therapies tested was particularly successful. These data nevertheless raise the hope that extending PFS would in turn extend OS, Dr. Lamborn concluded.

This analysis is ongoing. The same results were seen when the data were adjusted for age and performance status and when patients with prior surgery were excluded. Further analysis showed that response was predictive of survival with a hazard ratio of about 0.5. However, this did not alter the strength of progression vs. no progression as a predictor of survival. Analysis of a separate data set, involving patients with both Grade 3 and Grade 4 gliomas at first progression who were treated at the University of California, San Francisco, also concluded that progression status strongly predicted survival.

Dr. Lamborn then discussed the implications for sample size and study duration of using PFS vs. survival as an endpoint for studies aimed at regulatory approval. She estimated that a Phase 3 trial involving patients with Grade 4 tumors could be completed in 1.5 years if 6-month PFS was the primary endpoint vs. 3.5 years if OS was the primary endpoint. For a Phase 3 trial involving patients with Grade 3 tumors, the estimated study duration would be 2.5 years if 6-month PFS was the endpoint vs. 4.2 years if OS was the endpoint.

Dr. Buckner asked whether age, performance status, and extent of resection were associated with differences in PFS outcome. Dr. Lamborn replied that age was associated with PFS outcome much more strongly than was performance status. She did not look at extent of resection because few patients fell into this category. Instead, a second analysis was performed in which patients who had surgery within 30 days of the start of the study were excluded. This made no difference to the results of the analysis. Dr. Lamborn also responded to two other questions concerning the analysis methodology.

### **Panelist Discussion—Imaging-Based Outcomes**

Dr. Barker commented that the discussion about defining response and progression was in the context of no locally delivered therapy. It had not been explicitly stated that none of the reported findings apply to the measurement of response, progression, or PFS following carmustine wafer implantation. He added that trials in recurrent disease must have carefully defined starting points and entry criteria. Particularly for trials involving antiangiogenic agents in recurrent disease, goals for trial endpoints must take into account whether or not patients have measurable disease. All of the endpoints that have been discussed may also be starting points for certain other trials.

Dr. Loeffler noted that when patients are treated with escalating doses of radiation, post-treatment imaging of their tumors almost always appears worse than before, but in most cases these changes are transient. Dr. Fine said that the trials analyzed by Dr. Lamborn all involved chemotherapeutic or targeted agents that would not be expected to cause significant radiographic changes; thus, the findings of her analysis may be relevant only for certain classes of therapies.

Dr. Yung said this highlighted the problem of interpreting MRI data that are acquired close in time to the use of high-dose radiation therapy; in this situation, it is difficult to be sure of the meaning of radiographic changes. Dr. Provenzale commented that studies must take into account the expected effect of a drug or device on the underlying principles of the imaging technique being used; otherwise, conclusions may be misleading. For example, a therapeutic device implanted in the brain might cause changes in water diffusibility or in the permeability of the blood-brain barrier.

Dr. Yung noted that when the first scan is done 2 to 4 weeks after radiation therapy, a high percentage of observed changes are likely to be radiation-induced. One way to resolve this problem might be to discount the findings on this scan. The next scan 2 months later is likely to provide a more accurate picture of disease progression; determinations about discontinuing patients from the study on the basis of progression should be postponed until this point.

Dr. Fine asked whether any imaging modalities can definitively differentiate, for example, treatment-related from tumor-related changes in gadolinium enhancement. Dr. Patronas replied that from a morphological point of view it is not possible to distinguish treatment-related phenomena from tumor progression. Dr. Provenzale agreed that no single imaging tool could meet this need in all circumstances, but expressed hope that in any individual circumstance it might be possible to identify an imaging tool that would answer the question.

Dr. Fine pointed out that the focus of this discussion was whether any imaging modalities were currently validated to the extent that they could be reliably used to assess the efficacy of a drug. He said the data that had been presented suggested that PFS might be a valid predictor of survival (in the context of standard systemically administered agents), but the question was how progression is defined.

Dr. Paoletti said regional distribution of the lesion was an important issue; a 1 mm reduction in tumor volume in a certain part of the brain might have a dramatic clinical effect whereas a larger volume reduction elsewhere in the brain might be clinically meaningless. Companies engaged in drug development would like simple, clear guidance on how to measure disease progression because the RECIST criteria are not appropriate.

Dr. Buckner said the NCCTG data were reasonably convincing that either 1D or 2D measurement of contrast-enhancing tumor was a reasonable endpoint because both were associated with survival. He added that two independent data sets seemed to support the conclusion that, for patients with recurrent glioma who are treated with standard systemic agents, 6-month PFS is predictive of 12-month OS. He pointed out that the analysis of NCCTG data had excluded patients who were treated with stereotactic radiosurgery and implanted carmustine wafers. Additionally, the conclusions of the NCCTG analysis were not affected by inclusion in the database of patients treated with an agent with antiangiogenic properties. Although this agent was inactive according to the study definition, it may still have had biological activity. Dr. Buckner added that patients who have focal therapies are highly selected; for this reason, what could be a confounding variable was likely to be limited to a subset of patients.

Dr. Fine noted that the caveat regarding standard systemic agents was important. Two ongoing, industry-sponsored Phase 3 studies were using convection-enhanced delivery of the investigational agent and that necrosis and breakdown of the blood-brain barrier were anticipated toxicities. Thus, standard measures of radiographic progression (i.e., increased gadolinium enhancement) may not be predictive surrogates for overall antitumor activity or overall clinical benefit. He asked, however, whether it could be known with certainty prospectively that a new targeted agent would not cause MRI changes that would confound the measurement of progression. He added that it is not known whether or not antiangiogenic agents cause necrosis.

Dr. Yung said the data were convincing that 6-month PFS was a useful endpoint not only for recurrent disease but also for newly diagnosed disease. He asked if it was possible in multi-site trials to standardize the parameters for the use of contrast agents (e.g., how much contrast agent to use, the infusion rate, etc.). Dr. Fine asked whether inter-institutional variability in imaging was large enough to affect the results of a trial. Dr. Provenzale responded that in well-designed multi-site trials standardized criteria are used for imaging and compliance at individual sites is

monitored. Dr. Patronas said that the issue of different imaging equipment at different study sites could be addressed by prospectively designing imaging parameters and by requiring all scans of an individual patient to be done on the same instrument.

Dr. Fine asked the panelists whether, in large multi-institutional studies at their institutions, it was routine for a detailed MRI protocol to be followed. The consensus was that it was not. One panelist commented that at his institution a study evaluating contrast agents had failed because of cross-platform discrepancies. He felt that studies would fail unless imaging techniques were standardized across institutions.

Dr. Friedman asked whether studies could be designed in a way that allowed AA to be granted on the basis of interim results, with confirmation of clinical benefit provided (or not) by the final results of the same study. Dr. Pazdur said that FDA advocates this approach to trial design. One drawback, however, is that if the interim results show that the experimental agent appears to offer a benefit, crossover from the control arm may confound the final survival analysis. Dr. Pazdur added that the magnitude of a therapy's effect on an endpoint is an important consideration in regulatory decision-making. For example, a doubling of PFS would be a more compelling result than a 15% improvement.

Dr. Fine reiterated that the question before the panel was whether another endpoint was sufficiently accurate to replace or serve as a surrogate for survival, the current gold standard. Dr. Yung suggested that another way to phrase the question was whether the correlation between 6-month PFS and 12-month OS was significant enough to support the conclusion that the patient is likely to benefit from treatment. Dr. Buckner commented that the evaluation of survival is increasingly being confounded by the use of sequential therapies.

Dr. Provenzale said that the most appropriate technique for imaging and tumor measurement are likely to be different depending on whether scans are being performed at academic medical centers or at community-based centers. No single method will be optimal for all tumors. He recommended the use of two MRI techniques, one based on contrast administration and the second (performed at the same examination) not dependent on contrast administration. To enable the highest degree of confidence that imaging protocols will be followed, trials should be performed at tertiary care centers.

Dr. Fine noted that such a policy would have great implications for the way clinical trials are carried out in the United States. For example, the Radiation Therapy Oncology Group, which conducts most of the large Phase 3 trials in glioblastoma, has a large network of community-based investigators. Dr. Buckner suggested that the problem could be handled by requiring central image review, as occurs in pathology. Dr. Pazdur commented that it was problematic for FDA reviewers when there was a significant difference of opinion between image readers.

Dr. Pazdur asked whether panelists thought that freedom from disease progression constituted a clinical benefit to the patient in and of itself, regardless of whether it was a surrogate for overall survival. Dr. Buckner responded that freedom from progression would be valuable if it were known to result from the treatment, since other variables (e.g., age, performance status) are known to affect PFS.

Dr. Yung said that symptomatic deterioration often precedes radiographic evidence of disease progression. Dr. Fine added that disease progression cannot be defined only radiographically. A patient who is deteriorating clinically, even if shown to be progression-free by MRI scan at 6 months, would likely not feel that he or she was obtaining benefit from the current therapy. Dr. Yung pointed out that the NABTC criteria for lack of disease progression included stable neurologic condition. Dr. Buckner added that in the NCCTG clinical deterioration is considered disease progression even if the results of two consecutive MRI scans showed tumor stability.

It was noted that freedom from progression may result in freedom from therapy, which in brain tumors is often highly toxic, but that it may also be a result of concurrent chemotherapy; in the latter situation, freedom from progression may not be associated with improved QoL.

Several panel members said that no standardized scales are currently used to measure neurologic status. An assessment that a patient has deteriorated neurologically is based on clinical judgment. Dr. Yung noted that instruments used in other neurologic diseases (e.g., multiple sclerosis, dementia, stroke) measure highly specific aspects of neurologic function rather than global neurologic status.

Dr. Pazdur asked the panel if there are circumstances in which response rate would be a useful endpoint for brain tumor studies. He noted that in other tumor types FDA has accepted single-arm studies in which response rate was the primary endpoint. The advantages of single-arm trials are that they are generally less complex to design and require fewer patients. On the other hand, they cannot be used to characterize toxicity or evaluate time-to-event endpoints. Dr. Pazdur added that FDA had felt confident granting AA to temozolomide on the basis of response rate because several patients showed a sustained complete response. However, such sustained complete response rates are rare.

Dr. Buckner replied that if the response rate were of sufficient magnitude (e.g., greater than 30%), it was likely to be associated with clinical benefit; the magnitude of the response rate would outweigh the uncertainties associated with interpreting MRI scans. Dr. Yung said that several meta-analyses of data from negative Phase 2 trials in recurrent GBM had consistently found response rates of around 5% to 7% despite changes in MRI technology over time. Dr. Fine said that if response rate were the primary endpoint it would be important to select patients whose disease was clearly progressing. Dr. Crocker commented that it would also be important to ensure that post-surgical changes were not misinterpreted as a therapeutic response. Dr. Patchell said that the only two issues of ultimate importance for patients were survival and QoL.

### **Audience Questions and Comments**

Dr. Henry Brem, Johns Hopkins University, commented that all local therapies increase tumor enhancement and may very well increase diffusion; for this reason, MRI scans would be a poor way to assess the effectiveness of these therapies. He agreed with Dr. Patchell that improved survival and QoL were the key criteria to be met when assessing therapeutic effectiveness. Dr. Fine noted that the NABTC analysis did not exclude patients who received carmustine wafers as a first-line therapy.

Susan Arbuck of Schering-Plough, Inc., pointed out that the response rate that was the basis for AA of temozolomide was substantive but substantially below the rates that panelists had suggested might be required. The drug subsequently showed a survival benefit and received regular approval on that basis.

In response to a question from a member of the audience, Dr. Rock said that the EORTC study illustrated the value of survival as an endpoint. Six-month PFS was addressed in that study. The panel had heard some provocative, hypothesis-generating discussion about PFS this morning, he added. FDA would be interested to know how PFS maps with other prognostic indicators such as performance status and cognitive function. Dr. Buckner added that overall distribution of PFS was a secondary endpoint in the EORTC study.

Dr. Paoletti noted that many drugs now in development are not cytotoxic. For patients treated with these new-generation agents, stable disease or a minor response rate associated with symptomatic improvement may be very important. A new paradigm is needed for assessing the clinical benefit of these new agents.

Susan Wiener, a patient advocate with the NABTC, said that neurologic exams are indeed a solid measure, although there is no substitute for the physician's clinical judgment. Correlation between the neurologists' assessment and the patient's disease status would generally be high. She said she did not understand why a neurologic exam could not be included as a measure of the patient's response.

Dr. Buckner responded that it would be difficult to mandate a specific tool for use in the assessment of all patients; a global assessment of neurologic status might be more informative. Dr. Yung agreed. Dr. Fine said the development of a standardized neurologic assessment tool would be a worthwhile research effort but no tool currently exists that could be recommended for standard use.

Dr. Patchell said that in a recently completed trial in metastatic disease, clinical criteria and a custom-devised neurologic exam had been used to measure patients' neurologic status. An independent blinded committee reviewed the data and determined that the neurologic exam was as accurate as, and correlated closely with, investigators' clinical judgments of patients' status. Dr. Fine commented that other studies have shown that mental status or neurocognitive deterioration is a better predictor of long-term outcome than radiographic findings. Dr. Patchell said it would be helpful to have an objective scale that could be used across trials. He noted that neurologic function is closely associated with QoL.

## CLINICAL TRIAL ENDPOINTS FOR APPROVAL: PATIENT-REPORTED OUTCOMES

### Cognitive Testing and Patient-Reported Outcomes in Brain Tumor Clinical Trials (Dr. Christina Meyers)

Most patients with brain tumors suffer from cognitive dysfunction, Dr. Meyers said. The net clinical benefit of cancer therapy includes “beneficial effects on disease-related symptoms and/or quality of life,” according to an FDA-NCI working group. Maintaining function is particularly important for patients with brain tumors because long-term remission or cure is unlikely or is often accompanied by significant disability.

Clinical benefit to the patient with a brain tumor includes relief of tumor-specific symptoms, including disruption of brain function. However, anatomic evidence does not correlate well with cognitive function. A patient with a large, slow-growing tumor may have minimal cognitive impairment whereas a patient with a much smaller but rapidly growing tumor may have profound cognitive effects. Treatment-related changes on an MRI scan also do not correlate closely with patient function. For example, focal high-dose radiation therapy causes oxidative stress and inflammatory changes in the brain that may persist long after transient changes on an MRI scan have resolved.

Tumor-specific symptoms are measured by the patient’s subjective report of symptoms (headache, nausea, etc.), objective assessment of cognitive function or mood, and objective assessment of function (e.g., independence in activities of daily living). Clinical researchers evaluating cognitive function in patients with brain tumors want to know what if any cognitive problems the patient had prior to treatment and whether treatment regimens improve neurocognitive function as a result of better tumor control, slow expected tumor-related neurocognitive deterioration, and have more or less short- and long-term toxicity.

In a trial of a radiation sensitizer for the treatment of brain metastases, FDA stated that “radiological response alone is not acceptable for approval. However, improvement in neurocognitive function or delay in neurocognitive progression are acceptable endpoints.” These alternative endpoints are being used in ongoing and planned trials for both brain metastases and primary brain tumors.

**Assessment of cognitive function.** Evaluation of cognitive function presents a number of assessment issues. Performance status has little relation to cognitive function and QoL. Brief mental status exams are only sufficiently sensitive to detect serious cognitive impairments such as delirium and significant dementia. Self-reports of cognitive problems correlate poorly with objective test results; patients with brain tumors may have a diminished appreciation of their impairments and may report that their memory is fine when in fact they have significant memory deficits.

Any tool for assessing cognitive function must be brief (i.e., take no more than 30 minutes to administer) and repeatable in alternate forms with minimal practice effect. It must have good psychometric properties—that is, it must measure the intended function reliably over time. It

must be highly sensitive to changes in function, must measure relevant cognitive functions, and must be highly standardized and simple to administer. Most patients must be able to complete the instrument.

To be analytically valid, assessment instruments must reflect population norms—that is, must take into account the expected level of cognitive function in a patient of a specific age and educational level. The degree of change that is considered to reflect either an improvement or a decline in the patient’s performance must be prospectively established. Variation in results at different sites or by different examiners must be minimized; formal training, certification, and quality assurance requirements must be built into the trial. In trials of pediatric brain tumors, assessment instruments must be developmentally appropriate and must take into consideration the likelihood of altered long-term cognitive development.

Issues that may confound the assessment of cognitive function (e.g., adjuvant medications such as steroids, medical complications such as seizures) must be identified. Cognitive assessments should be performed at the same time intervals as other staging evaluations such as MRI scans. The frequency of assessment should be relevant to the disease course; for example, assessments may be less frequent in a trial of low-grade glioma than in a GBM trial. The results of cognitive assessments must be correlated with anatomic response and neurologic outcome, although cognitive deterioration may occur before other evidence of progression is apparent.

**Patient-reported outcomes.** Ideally, a patient-reported outcome (PRO) should be based on disease- or treatment-related symptoms rather than on social function or satisfaction with life. It must have sound psychometric properties, be simple enough to be completed by patients with cognitive deficits, and be sensitive to changes over time.

Several caveats apply to the use of PROs in patients with brain tumors. Patients need to have sufficient cognitive function to complete the instrument. Many symptom assessment instruments have suboptimal psychometric properties (e.g., poor test-retest reliability). Instruments must be able to account for reporting bias so that over- and under-reporters do not simply cancel each other out. Proxy assessments are problematic for subjective symptoms; for example, a caregiver cannot reliably evaluate the severity of a patient’s headaches. To reduce missing data, investigators must “buy in” to both cognitive and symptom assessment and encourage patients to complete the instruments. Finally, change in QoL does not parallel cognitive change and cannot be used as a proxy for it.

**Standardized approach to assessment.** In brain tumor clinical trials it is desirable to be able to compare cognitive and symptom assessment findings in trials of different agents conducted by different investigators. One of the recommendations of the NCI’s Brain Tumor Progress Review Group was to develop a “practice guideline protocol,” which would include standard content that would enable investigators to select the tools most appropriate for the evaluation of a specific drug or hypothesis.

**Which trials?** Several issues should be considered in deciding in which trials to use cognitive and symptom assessment as endpoints. For randomized controlled trials, cost effectiveness and whether alternative endpoints should be primary or secondary endpoints are among the issues to

be discussed. It may also be worth considering what value alternative endpoints might add to single-arm Phase 1 or Phase 2 trials. For example, they could be useful in monitoring neurotoxicity. Standard content would permit comparison of findings from different single-arm trials.

### **Panelist Discussion—Patient-Reported Outcomes**

Dr. Pazdur noted that PRO endpoints have been incorporated into many cancer clinical trials in other tumor types, but to date few trials have succeeded in demonstrating a beneficial impact on patients' QoL. There are methodological challenges to the use of PRO endpoints in cancer trials. For example, sponsors often submit to FDA only a single, unblinded, randomized trial with a lot of missing data. Dr. Pazdur emphasized that FDA believes patient QoL is an important outcome in cancer treatment. However, if PROs are to be used as the basis for drug approval, they must be measured with the same rigor as any other endpoint.

Jane Scott, Ph.D., FDA endpoint reviewer, drew a distinction between general QoL (e.g., financial security, quality of personal relationships) and health-related QoL (HR-QoL), which is the aspect that FDA reviewers focus on. HR-QoL is a multidimensional concept that encompasses, but is not necessarily limited to, measurement of symptoms and physical function. However, the ability to accurately measure the impact of a therapy on symptoms would be valuable to FDA even if it could not be directly related to improvement in patient function.

Dr. Scott asked whether panel members have been developing tools that have proved helpful in systematically establishing what a patient's symptoms are and how they change over time. Dr. Meyers replied that a symptom research group at M.D. Anderson Cancer Center, of which she is a member, has developed several psychometrically based symptom assessment tools, which she has used in brain tumor clinical trials. In one recently published trial, patients' symptoms were unchanged except for fatigue, which worsened considerably.

Dr. Scott noted that in other tumor types there is less reason to be concerned that the disease process itself and/or its treatment will erode patients' cognitive function. She asked for information about efforts to develop standardized clinician assessments of patient symptoms and function to complement patient self-reports and about study designs that would enable patients' symptoms and function to be followed as their disease advances. Dr. Meyers acknowledged that self-reported symptom assessments in patients with brain tumors present a high risk of selection bias because only the more highly functioning patients can complete them. Some steps can be taken to compensate for patients' deficits, such as reading questions aloud to patients who have difficulty reading. Patients with the worst cognitive function (who, for example, cannot rate their pain on a numerical scale) most likely will have been withdrawn from the study.

Dr. Scott asked if it would be feasible to design trials so that findings on patient self-reported symptom assessments and objective cognitive tests would trigger radiographic assessment, rather than performing radiographic assessments at fixed time intervals. Dr. Meyers responded that this study design had not been tried at M.D. Anderson for logistical reasons, since patients often have to travel long distances to attend their assessments.

Dr. Pazdur asked for comments on the feasibility of designing a composite endpoint that combined measures of patient function with radiographic findings. Dr. Crocker noted that other factors, such as a patient's dose of seizure medication being too high, could confuse the assessment of patient function. A composite endpoint that combined "soft" endpoints would not be helpful. Dr. Meyers said she knows of trials that have stipulated that a change in function be confirmed at a subsequent assessment to increase confidence in the finding.

Dr. Barker commented that it would be helpful to distinguish whether data were missing because patients were too ill to attend the assessment or because it was inconvenient for them to attend. Dr. Friedman observed that clinical and radiographic findings can be contradictory (i.e., the MRI scan can look good but the patient is clinically worse, or vice versa). Dr. Paoletti urged that an effort be made to develop and validate standardized tools.

Dr. Rock asked Dr. Meyers to describe the metric she developed for trials of motexafin gadolinium (Xcytrin) in patients with brain metastases. Dr. Meyers said that in those trials patients had been assessed monthly with a brief battery of tests that took about 23 minutes to administer. The memory test had six alternate forms. Other tests focused on measuring patients' independence in activities of daily living (e.g., frontal lobe function, motor coordination). Careful certification procedures were employed to ensure the accuracy of test administration. The tests was translated into multiple languages and administered to patients in 7 countries. Multiple comparisons were performed. A test focusing on a single aspect of cognitive function is insufficient because patients will develop different symptoms (e.g., weakness, headaches) depending on factors such as the location of the tumor. Memory function tends to be most sensitive to both tumor and treatment effects.

Dr. Pazdur observed that symptoms can more readily be measured when a particular symptom is a cardinal feature of the disease (e.g., dysphagia in esophageal cancer, bone pain in prostate cancer). Symptoms that are diffuse or ill-defined, or that do not appear until very late in the disease course, are much more difficult to measure. Dr. Yung said that the fact that a patient's symptoms are so dependent on the location of their tumor has so far confounded efforts to develop a standardized approach to symptom assessment in brain tumors. Dr. Lamborn asked if it was possible to prospectively define and follow symptoms on an individual-patient basis. Dr. Meyers said she had no experience with this approach.

Dr. Fine observed that high doses of steroids are a major cause of morbidity in patients with brain tumors. Steroid doses are determined empirically by attempting to find the lowest dose that optimizes the patient's neurologic function. A nontoxic drug that stabilized the vasculature and enabled patients to take lower doses of steroids would provide clinical benefit even if it had no effect on the tumor itself. He asked how a trial of such an agent could be designed to reliably capture this benefit. Dr. Pazdur said such a trial would have to convincingly demonstrate a beneficial effect on steroid doses and on the toxic side effects of steroids. Measuring such changes consistently in an unblinded trial could be challenging. Dr. Scott added that the use of a validated, standardized approach to symptom measurement would be helpful in such a trial design.

Dr. Pazdur noted that PROs have been the basis for approvals of drugs in other therapeutic areas such as neurology and psychiatry. In these cases, however, the approval decision is usually based on review of two blinded, randomized trials. Blinding of trials is problematic in oncology because of factors such as different drug delivery schedules, different toxicities, and patient reluctance to enter blinded trials. Additionally, in most cases, a single pivotal trial is submitted. When the magnitude of change attributable to a new therapy is relatively small, it is difficult to be confident that a beneficial effect on symptoms or QoL is not due to chance or to a placebo effect. Another common problem is that in many trials assessments of PROs and QoL are added on as an afterthought instead of being integrated into the trial.

Dr. Pazdur asked Dr. Scott to describe the factors that reviewers in other therapeutic areas take into account when considering an application for approval based on PROs. Dr. Scott said that in many therapeutic areas reduction or stabilization of symptoms is regarded as an important clinical benefit. It is important at the outset to clearly define the symptom that is to be measured, which sounds simple but in practice can be very nuanced. In particular, patients must understand what is being measured. Symptoms that clinicians consider important may not be the ones that are most bothersome to patients.

The next step is to test the questions to ensure that patients understand them and to try the questionnaire out in studies. A large literature has evolved on the development, calibration, and validation of questionnaires. The literature also addresses what kind of recall patients can reasonably be expected to have of past events. For patients with brain tumors, a disease in which both the condition and its treatment may significantly affect memory, the focus should to the extent possible be on asking patients about their current status. When questionnaires are translated into other languages, care must be taken to ensure that patients' scores are not affected by the language in which they respond to the questions.

Dr. Scott added that in her experience FDA has found symptom and HR-QoL assessments to be most helpful, reliable, and useful for regulatory purposes when the findings are derived from double-blinded randomized trials. It would be problematic, in her opinion, to accept symptomatic improvement as the primary grounds for approval on the basis of a single unblinded study.

Dr. Weiss noted that in rheumatoid arthritis a composite instrument has been developed and validated that combines measurement of symptoms with objective measures of the patient's status. Dr. Scott said that all composite measures must be based on a large amount of data so that reliable judgments can be made as to what the parameters of each element should be. Some questionnaires sacrifice precision to achieve brevity. Some composite instruments combine several different measures into a single global score, making it difficult to pinpoint the precise areas in which the patient obtained benefit. The ability to disaggregate a global score is an important feature of any composite measurement tool.

### **Audience Questions and Comments**

Dr. Elana Farace, Penn State University, stated that she held an NIH grant to study the relationship between global QoL and neurocognitive symptoms over time in patients with malignant glioma; Dr. Meyers is her senior mentor on this grant. She said the discussion at the

morning session suggested that clinicians felt they could assess a patient's overall status on the basis of detailed information about neurological and neurocognitive function, whereas FDA seemed to be talking about global QoL. The latter is more difficult to assess and there is a lack of information about the relationship between neurological/neurocognitive function and QoL. Her data suggest that deterioration in neurocognitive function adversely affects QoL more seriously than does decline in physical function. She added that a large body of data supports the reliability and validity of standardized neuropsychological tests.

In response to a question from a member of the audience, Dr. Scott said that the usefulness of a patient's KPS score often depends on whether the patient was initially high-functioning or low-functioning on the KPS scale. Low-functioning patients may be unable to self-report symptoms and cognitive tests may be a less useful measure of their status. In any case, the KPS score is usually only modestly correlated with patient self-reported symptoms. Dr. Meyers added that the psychometric reliability of the KPS is low; in one published study, there was only 29% agreement between two physicians on what a patient's KPS score was.

Dr. Fine said that both the KPS and the Eastern Cooperative Oncology Group performance status scales were developed for systemic tumors and were essentially surrogates for tumor burden. Because these scales tend to focus on motor function rather than cognitive function, they are unreliable tools for the assessment of patients with primary brain tumors.

Dr. Pazdur said FDA's experience with global QoL measures in other disease areas has been unsatisfactory. He said the agency has in the past suggested to sponsors that they measure time to symptomatic progression rather than time to radiographic progression, using blinded evaluators to minimize bias. He said that patients could continue to be followed for time to symptomatic progression even after a change in therapy, just as patients' survival continues to be monitored after a change in therapy. He asked for comments on this approach. He stressed that FDA is very interested in the use of PROs as endpoints, recognizing that symptoms are a very important issue for patients.

Dr. Fine responded that this approach would require a large randomized trial in which tumor location was controlled for, since tumor location has such a significant effect on the patient's symptoms. Dr. Patronas noted that in his experience symptomatic deterioration may occur before disease progression is evident on the patient's MRI scan. Dr. Crocker said it would be important to correlate symptomatic progression with survival. Dr. Buckner said such an endpoint would be very valuable and would probably have a high rate of acceptance but he questioned whether a validated tool currently exists to measure it.

Dr. Kun said the data do not yet exist to document that measurable changes in patient symptoms can be correlated with progression, PFS, or survival in any population with brain tumors. Dr. Yung said the cognitive-function battery described by Dr. Meyers has been validated, but there is a lack of experience in large randomized trials to confirm that it is a valid surrogate. Dr. Meyers noted that the battery has been validated in brain metastases. She added that treatment neurotoxicity (e.g., late radiation effects) is an additional complicating factor. Ms. Wiener (patient advocate) suggested that neurocognitive function might be an appropriate topic for an NIH consensus conference.

Dr. Scott emphasized that in FDA’s view the reliable demonstration of a reduction in patient symptoms is a clinical benefit in and of itself, regardless of the long-term survival benefit associated with the therapy. Measurement of symptoms can also be helpful in establishing the appropriate next step (e.g., imaging studies), but the requirement that these be perfectly correlated tends to minimize the value of the outcome itself.

A member of the audience questioned whether the benefit of extending survival may be overestimated when the patient’s neurocognitive function is seriously compromised. Tom Nesi, patient representative on the panel, responded by noting that he had cared for his wife, a GBM patient, for 18 months. In his opinion, survival was not a good outcome measure. He said his wife was unconscious for the last 4 weeks of her life. Caregivers and primary care providers would certainly question whether extending survival is always beneficial, he said.

Mr. Nesi added that assessment of the quality of a patient’s life must take into account issues such as the effect of polypharmacy (during her illness his wife was taking at least 7 prescription medications); the impact of a sudden, lethal diagnosis on a previously healthy person and on his or her family; and the enormous financial burden of treating the disease.

Dr. Grant Williams, Novartis Corporation, from the audience, suggested that since both symptom progression and imaging progression seemed to have drawbacks as sole endpoints, the solution might be to combine them—that is, to define disease progression at 6 months by means of both symptom and imaging progression.

## **GENERAL PANEL DISCUSSION**

Panel members turned their attention to the general discussion questions posed by FDA.

### *Individual Endpoints*

#### *1.1. What if any non-survival endpoints reflect or predict clinical benefit?*

The panel agreed that 6-month progression-free survival (PFS) (with clinical stability as currently defined and without the use of local therapies) is a meaningful endpoint.

#### *1.2. What if any endpoints available now may be reasonably likely to predict clinical benefit?*

Dr. Pazdur said the term *reasonably likely* refers to surrogate endpoints that are “reasonably likely to predict clinical benefit,” the standard for granting accelerated approval (AA). Symptomatic improvement would be considered direct clinical benefit to the patient, not a surrogate for clinical benefit, and could therefore be used as an endpoint for regular approval.

Dr. Buckner said the neuro-oncology community has accepted radiographic response as a surrogate endpoint in oligodendroglioma because the magnitude of the benefit was dramatic and it was unequivocally treatment-related. Radiographic response is a reasonable endpoint if it convincingly represents a therapeutic effect, he said. Dr. Fine added that the response should be significant (i.e., greater than 15% or 20%) and durable, the patient must be clinically stable or

improving, and the patient's doses of steroids must be stable or decreasing. Dr. Yung said it was generally established that a response must be validated on a second scan.

Dr. Barker asked whether it was necessary to stipulate how one knows that a response is treatment-related. Dr. Provenzale said that the effects of therapy on imaging of the patient's tumor must be understood. Imaging studies, in his opinion, are reflectors of therapy rather than predictors of outcome. Dr. Yung said that because agents are now in use that modify the blood-brain barrier and change edema patterns, outcome measures must correlate with a therapeutic agent's biologic activity. Dr. Fine said the agent's mechanism of action must be considered in determining an appropriate surrogate endpoint; one surrogate is unlikely to be appropriate in all circumstances.

Dr. Pazdur said that the magnitude of response (including the number of complete responses) is important, particularly in a disease characterized by inter-reader variation in response assessment. The presumed effect of a drug is often overestimated; an agent may look promising in a small study, but in a larger trial response rates may be much lower.

Dr. Kun commented that many novel agents such as angiogenesis inhibitors may stabilize disease but not cause tumor shrinkage, which is the conventional means by which response is measured. Dr. Pazdur noted that some recently approved agents had low response rates but large effects on time to progression. He noted that although response can be measured in a single-arm study, time-to-event endpoints must be measured in randomized trials.

*1.3 Is it reasonable to allow a period of time for a novel biologic agent to have a biologic effect on a tumor? If so, how much time is reasonable?*

Dr. Rock said that this question was specifically relevant to the use of novel biologic therapies that are locally delivered at a tumor site and may initially result in images that appear to show radiologic tumor progression. In response to an earlier comment by Dr. Provenzale regarding the difficulty of making blanket statements about response based on novel MRI techniques, Dr. Rock said FDA did not find this to be a limiting factor. He said the Office of Oncology Drug Products invites drug sponsors to come in at any time to discuss endpoints that they are considering using in registration trials.

Dr. Barker said he believed that initial imaging changes associated not with biologic therapies but with standard external beam radiation can be significant in predicting survival. He said it is increasingly clear that imaging changes that develop during or soon after treatment are an unreliable guide to a patient's prognosis following local therapy and should be interpreted with considerable caution. To improve understanding of the effects of local therapies, including their biological effects, careful consideration should be given during trial design to how much apparent "progression" can be tolerated and for how long before the decision is made to proceed with interventions such as PET scanning or biopsy.

Dr. Lamborn suggested that two separate issues must be differentiated: firstly, the need to ensure that a temporary effect of treatment on imaging is not misinterpreted as disease progression; secondly, the fact that certain agents may require a period of time after delivery before their

effects become apparent. From a statistical perspective, it is acceptable to prospectively plan for allowing some time to elapse before counting apparent radiographic progression as disease progression. In this circumstance, however, it would be necessary to re-evaluate the historical data on PFS that she and Dr. Ballman had presented.

Dr. Yung noted that it may take 8 to 12 weeks for an antiangiogenic agent to exert a modulating effect on the tumor angiogenesis environment. The oncology community has debated the period of time that such agents can be given to patients before it is concluded that they are ineffective. In brain tumor therapy no standard approach to this problem has yet been agreed on.

Dr. Fine said that he knew of very few examples of patients who had been retained on therapy despite apparent evidence of progression who had subsequently responded to therapy. Dr. Pazdur noted that several drugs now used in oncology are continued after progression has been documented; in some but not all cases, this approach was prospectively planned in the studies that led to the drugs' approval. Dr. Meyers pointed out that the patient obtains no benefit from a therapy if his or her condition declines irreversibly during the time spent waiting for a drug to exert its effect. Dr. Buckner suggested that time to treatment failure might be an appropriate component of a composite endpoint.

Dr. Yung said it would be reasonable to allow time for certain classes of drugs to work even if there is apparent radiographic progression, provided that the patient remains clinically stable. Dr. Barker said it would be important to measure the symptomatic deterioration and weigh that against the potential eventual benefit of the therapy.

### Composite Endpoints

#### *2.1. What evaluation techniques discussed are complementary?*

Dr. Pazdur said that the information FDA sought with this question was whether it would be reasonable to accept a composite endpoint that, for example, combined the findings of two radiologic tests (e.g., MRI and PET), or that combined radiologic and clinical endpoints, or that combined a radiologic endpoint with symptom measurement or patient-reported outcomes (PROs). Dr. Lamborn said that PFS was already a composite endpoint, although its precise components had not been documented.

Dr. Rock asked for comments from the panel on the cognitive function metric described by Dr. Meyers, which she had developed for trials of motexafin gadolinium (Xcytrin) in patients with brain metastases.

Dr. Paoletti observed that the role of PET had not been highlighted in the panel's discussions. Dr. Patronas responded that PET may be useful in some situations to supplement the information obtained from MRI or clinical evaluation but that it has not been validated to assess treatment response in brain tumors. He therefore could not recommend routine use of PET for this purpose in prospective studies. Dr. Provenzale agreed that it would currently be premature to use PET in Phase 3 studies in brain tumors but said it would be helpful to gather exploratory data on the use of PET in well-controlled Phase 2 studies. Dr. Yung said that resolution is currently inadequate in FDG-PET images of brain tumors. Dr. Fine said that PET has an important role to play in

understanding brain tumor biology but cannot be recommended for use in registration studies at this time.

Dr. Buckner said that given uncertainty about whether imaging changes are clinically meaningful in all circumstances, it would be helpful if radiographic evidence of a therapeutic effect could be complemented by evidence of functional or symptomatic improvement.

### Endpoint Development

#### *3.1. What if any potential endpoints should be explored apart from those discussed?*

Dr. Fine observed that although the panel had not discussed the role of molecular and other biologic markers for segregating patient populations, such markers will play an increasingly important role not only in study design but also in the approval process for drugs to treat brain tumors as well as other cancers.

#### *3.2. What questions should be brought from this workshop to the Oncologic Drugs Advisory Committee (ODAC) for further consideration?*

Dr. Pazdur said that ODAC should be asked to consider whether 6-month PFS is an established surrogate for clinical benefit in brain tumor studies or a surrogate that is *reasonably likely* to predict clinical benefit (the standard for granting AA).

Dr. Yung said that ODAC should also be asked to consider the question of whether unidimensional, bidimensional, or volumetric approaches to tumor measurement are optimal. Dr. Provenzale added that some volumetric measurement techniques are highly reproducible and have a low rate of inter-reader variability, a factor that should be considered if such variability is a concern.

Dr. Fine said that ODAC should be asked whether a profound radiographic response rate in a single-arm trial should be considered a surrogate endpoint that is reasonably likely to predict clinical benefit.

Dr. Lamborn suggested that a significant increase in 6-month PFS in a single-arm trial (e.g., 40% vs. 15%) might also be considered a surrogate endpoint that is reasonably likely to predict clinical benefit. Dr. Pazdur responded that, whereas response rate can be unequivocally considered to be a direct therapeutic effect, disease stabilization is influenced by many factors in addition to the experimental therapy. Randomization is the best way to account for such unknown factors. Because FDA must be satisfied that a drug truly has a therapeutic effect before approving it for marketing, the agency has been reluctant to accept time-to-event endpoints in single-arm trials.

Dr. Weiss said consideration should be given to the importance of obtaining confirmatory data after AA has been granted. Once a drug has been approved, however, it is often difficult to complete the trials necessary to confirm clinical benefit. Dr. Fine noted that in a rare disease such as a primary brain tumor, in which patients have few treatment options, it is difficult to recruit patients to randomized trials because the standard treatments offered in the control arm are

unattractive. Dr. Pazdur said this problem can be addressed by, for example, studying the drug in combination with another therapy (e.g., radiation) in the adjuvant setting or by conducting the confirmatory trial outside of the United States in a country where the drug is not yet approved.

Dr. Weiss asked Dr. Meyers for her suggestions on how to frame questions about PROs and symptom measurement for discussion by ODAC. Dr. Meyers responded that in addition to measuring response to therapy, neurocognitive function should also be measured in Phase 2 trials to provide information about possible injury to normal brain tissue.

### **Audience Questions and Comments**

A member of the audience commented that targeted therapies may be most effective in subsets of patients. He asked what sort of metrics FDA would consider meaningful in a study testing a targeted therapy in a patient subset. Dr. Pazdur responded that this question would require a longer discussion than was possible at this meeting. In general, one would expect to see an above-average therapeutic effect when a targeted therapy is used in a patient subset; for this reason, endpoints other than survival could be considered. However, the agency has not clearly defined what endpoints it would consider specifically for targeted therapies.

Ms. Wiener (patient advocate) said that ODAC should be asked to consider rethinking the endpoints for brain tumor trials so that “longer life” and “better life” are not alternatives but are integrated (“longer life if it is better life”).

### **WORKSHOP SUMMARY (Dr. Henry Friedman)**

Dr. Friedman summarized the workshop proceedings, focusing on the following questions:

- *Can a unified set of outcome assessments be applied to primary brain tumors as a group?*

There was a consensus among panel members that 6-month PFS was an endpoint that should be pursued in trials in the near future.

- *How well do existing and imagined imaging techniques assess or predict clinical benefit?*

Imaging techniques assess or predict progression reasonably well, although there are concerns about reproducibility. They assess or predict response less well, except in the case of complete responses or a dramatically high response rate.

- *Might a unified PRO metric be validated to assess clinical benefit across both multiple therapeutic approaches and types of primary brain cancers?*

There was consensus among panel members that PRO metrics are not yet sufficiently developed to be acceptable in registration trials in primary brain tumors.

In response to the comments made by Mr. Nesi (patient representative), Dr. Friedman said that every clinician who treats patients with brain tumors does so with the hope that each patient will

achieve longer survival accompanied by QoL that the clinician would find acceptable for a member of his own family. Extended survival with poor QoL is not a satisfactory outcome. Dr. Friedman suggested that FDA review studies with a view to trying to ensure that improvements in survival are not achieved at the expense of QoL. He added that PFS may be a better endpoint in terms of assuring acceptable QoL because, in his experience, it is uncommon for patients to deteriorate clinically while their tumor is under control.

## **BIOMARKER AND ENDPOINT RESEARCH PRIORITIES**

Questions for discussion:

- *Which endpoints appear most promising and ready or nearly ready for clinical/regulatory application?*
- *What strategies are required to validate the most promising endpoints?*
  - *Are there ongoing or planned clinical trials that could incorporate these endpoints to facilitate validation?*
- *What are the most promising strategies to identify the next generation of promising endpoints/biomarkers for development?*
  - *What are the leading candidates for near-term development?*
- *How should the various promising imaging modalities be developed as biomarkers?*

Dr. Pazdur welcomed attendees to the final workshop session, the purpose of which was to identify endpoint-related issues that should be taken forward into new or existing clinical trials. The discussion was led by Dr. Jeffrey Abrams of NCI's Cancer Therapy Evaluation Program, Dr. Lalitha Shankar of NCI's Cancer Imaging Program, and Dr. Tracy Lugo-Lively of NCI's Cancer Diagnosis Program.

Dr. Abrams said that in brain tumors, the most promising potential endpoints (and those that were the focus of the most discussion during this workshop) seem to be imaging tests and HR-QoL endpoints.

Dr. Abrams noted that NCI's research program in brain tumors is fairly extensive considering the uncommon nature of the disease. NCI supports four Specialized Programs of Research Excellence in brain tumors, two research consortia on brain tumors in adults, and one research consortium on pediatric brain tumors. In addition, several of the NCI-supported cooperative groups, including the American College of Radiology Imaging Network, conduct research on brain tumors. NCI's Cancer Diagnosis Program supports a program for prognostic assessment of clinical cancer tests and the Cancer Imaging Program supports an imaging implementation group. NCI's Division of Cancer Control and Population Sciences supports an HR-QoL initiative.

Dr. Abrams said NCI would welcome opinions on where it should be investing in trying to bring new therapies to patients with brain tumors. For example, should the priority be to incorporate new imaging tests or neuropsychiatric tools early in drug development or to maximize the benefit to patients from drugs such as temozolomide? Should imaging tests focus on measuring tumor shrinkage or on functional imaging? Which imaging techniques should be used?

Dr. Shankar noted that the Cancer Imaging Program is funding several large imaging studies through its grants portfolio and is working to address significant issues such as standardization and validation in the clinical setting that currently impede the use of radiographic studies. Workshops have taken place in an effort to achieve consensus on the use of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and FDG-PET. Consensus guidelines on the use of FDG-PET were issued in 2005 and are now being applied prospectively in all NCI-sponsored trials in which that technique is used. In November 2004 consensus was achieved on the use of DCE-MRI for body imaging; however, discussions are continuing on the use of this technique for brain imaging. NCI is working with the American College of Radiology to update existing guidelines on a 3-yearly cycle to ensure that they reflect current technology.

To address the logistical difficulties and costs associated with archiving and central reading of images, NCI is working to provide electronic image archiving for prospective studies and to enable images to be accessed and read centrally via the Internet. Experience from multiple trials has shown that central reading of images results in a more reproducible response rate. Data security will be employed to ensure that only investigators involved in a trial can access the data. Archived data that have been anonymized and annotated with clinical information will be available to the research community. NCI is also supporting pilot and early-phase studies to evaluate novel imaging agents.

Dr. Lively said that her branch's research portfolio is focused on the development of tissue- and serum-based prognostic and predictive markers. Most of these markers are not yet sufficiently well developed to be germane to the questions faced by today's panel. Nevertheless, NCI felt it was important for panelists and workshop attendees to be aware of ongoing research in this area. The Diagnostic Evaluation Branch supports both independent research projects and correlative studies associated with clinical trials to discover or confirm the importance of molecular or biochemical markers that could be useful in clinical decision-making. Experience with the approval of targeted agents to treat solid tumors has shown that diagnostic or predictive assays to guide the use of an agent need to be tested and validated before pivotal Phase 3 trials aimed at registration of an agent are begun.

Dr. Abrams asked the panel to suggest what critical trials NCI should be supporting in brain tumors. Dr. Pazdur asked for information about ongoing and proposed Phase 3 trials and the feasibility of embedding endpoints such as 6-month progression-free survival (PFS), neurocognitive testing, or time to symptomatic progression into these trials. Dr. Abrams responded that the only currently ongoing trial is a Radiation Therapy Oncology Group (RTOG) trial comparing intravenous carmustine with temozolomide as adjuvant therapy in high-grade gliomas; this trial has run into difficulty because of a shortage of intravenous carmustine and consideration is being given to converting to oral lomustine.

A large Phase 3 trial (RTOG-0525) comparing standard-dose with dose-dense temozolomide as adjuvant therapy for high-grade gliomas has just been launched in collaboration with the European Organization for Cancer Research and Treatment (EORTC). A Phase 3 trial is planned to compare the effectiveness of temozolomide in patients with and without deletions of

chromosome 1p and/or 19q. Other trials that are being considered would evaluate the role of temozolomide in subsets of patients such as the elderly and those with low-grade gliomas.

Dr. Yung said that RTOG-0525 had been designed with survival as the primary endpoint. It would be feasible to evaluate the correlation between 6-month PFS and overall survival in this trial. RTOG is submitting a separate grant application to evaluate the correlation of biomarkers with response and the effect of treatment on biomarkers. However, this might not be an appropriate trial in which to evaluate DCE-MRI because temozolomide is not a drug that modulates permeability and perfusion.

Dr. Fine said that Phase 3 trials provide a platform for the evaluation and validation of surrogate endpoints; the endpoints need not be related to the study drug. Evaluating endpoints in small groups of patients or in single-arm trials provides no information about the natural history of the disease or about how the endpoints might change in the presence of an effective therapy; evaluating endpoints in Phase 3 studies can address these limitations.

Dr. Abrams suggested that 6-month PFS could be studied as a secondary endpoint at a subset of centers participating in the RTOG trial that have the ability to standardize MRI scans. Dr. Pazdur said that it should be relatively simple to collect data for a “single point in time” endpoint such as 6-month PFS.

Dr. Pazdur added that because neurocognitive dysfunction is a cardinal feature of primary brain tumors, it is important to gain experience with neurocognitive testing in Phase 3 trials. Dr. Yung noted that the neurocognitive battery developed by Dr. Meyers had been validated in brain metastases in large trials supported by industry and by EORTC. Neurocognitive testing could be incorporated into any large trial provided that additional resources were made available to do it.

Dr. Paoletti said that industry would be willing to participate in the development and validation of neurocognitive testing instruments in Phase 2 and 3 randomized trials. He added that it is also extremely important to develop standardized ways of assessing patients’ neurologic status and to try to correlate neurologic status with the site of the lesion. Industry would also appreciate guidance from NCI on the optimal approach to take to tumor measurement.

Dr. Barker said he suspected that some drugs now being tested as anti-tumor agents would fail in that capacity but would nevertheless reduce the volume of edema surrounding the enhancing mass and perhaps the apparent size of the tumor itself through the restoration of the disrupted blood-brain barrier, thus relieving symptoms; as such, they could be potential replacements for steroids. This issue could be addressed in small Phase 2 trials if the appropriate methodology existed to standardize across centers the measurement of neurologic changes and the measurement of vascular permeability, volume of peritumoral edema, and enhancing volume.

Dr. Abrams noted that for trials in low-grade gliomas, in which survival is not a useful endpoint, the NCI-supported cooperative groups are trying to develop an HR-QoL instrument that could be used either as a primary endpoint on its own or could be combined with an objective measure into a composite endpoint. At present different groups tend to favor different instruments. There is a need to develop validated instruments that are widely accepted.

Dr. Fine noted that most Phase 3 clinical trials in gliomas are exclusively supported by industry. He asked if it would be feasible for CTEP to fund an investigation of a particular potential endpoint within an industry-supported Phase 3 trial. Dr. Paoletti said he believed industry would be willing to collaborate in this way provided that agreement could be reached on intellectual property issues. Dr. Abrams said this would be a new mechanism for CTEP but he saw no reason why an effort could not be made in this direction. He noted that investigators in the NCI-supported brain tumor consortia work collaboratively with industry on many Phase 2 trials.

In response to a question from Dr. Yung, Dr. Shankar said that NCI is supporting a demonstration project in renal cell carcinoma to test the reliability of DCE-MRI in predicting treatment response and the feasibility of using DCE-MRI in a multi-center study. One hundred out of 300 patients enrolled in the study will receive DCE-MRI. Centers performing DCE-MRI must do so in accordance with trial guidelines and must meet quality assurance standards. Consideration could certainly be given to undertaking a similar study in a subset of patients with brain tumors.

Dr. Yung noted that the brain tumor consortia are currently running several large Phase 2 trials to evaluate agents in the class of tyrosine kinase inhibitors. When the consortia have proposed adding sub-studies to evaluate DCE-MRI, barriers have arisen related to funding or to concerns about the uniformity of imaging. Dr. Abrams responded that funding constraints necessitate limits on the use of MRI in NCI-supported trials. The challenge is to try to identify the trials in which the use of MRI is most likely to move the field forward. Dr. Shankar commented that in a trial in which patients are being routinely evaluated via MRI, the addition of a DCE-MRI evaluation components would add only 15 minutes to a patient visit.

### **Audience Questions and Comments**

A member of the audience commented that a large amount of neurocognitive data already exists from completed trials. She asked whether NCI would be interested in funding a secondary analysis of this data to address some of the questions that had been raised during the panel meeting. Dr. Abrams said this sounded like a good idea and a good way to extract the maximum information from Phase 3 trials. He added that NCI's Division of Cancer Control and Population Sciences might have initiatives in this area of which he was unaware. Dr. Fine cautioned that existing data are relevant to brain metastases of systemic tumors, which have a very different biology and growth characteristics than primary brain tumors. It is therefore unclear whether analysis of neurocognitive and symptom-assessment data from patients with brain metastases will advance the knowledge base concerning primary brain tumors.

Another member of the audience noted that there are reasons to think volumetric measurement of irregularly shaped tumors may be more accurate than measurement of tumor diameter. He asked if it would be possible to evaluate the accuracy of the measurement methods used for images stored in the imaging archive that NCI is developing. Dr. Shankar responded that this issue is still under discussion.

### **Adjournment**

Dr. Pazdur thanked the panelists, NCI representatives, and audience for their participation. The workshop was adjourned.

## Challenges and Considerations in Linking Adult and Pediatric CNS Malignancies

Henry S. Friedman, MD  
The Brain Tumor Center at Duke

## What is the relationship between adult and pediatric CNS tumors?

Are there compelling similarities or  
differences in pediatric and adult CNS tumors  
which can guide application of the Pediatric  
Rule of 1998.

### Histologic Classification of Tumors of the CNS

#### Tumors of neuroepithelial tissue

- Astrocytic tumors
  - Astrocytoma
  - Anaplastic astrocytoma
  - Glioblastoma multiforme
  - Pilocytic astrocytoma
  - Pleomorphic xanthoastrocytoma
  - Subependymal giant-cell-astrocytoma
- Oligodendroglial tumors
  - Oligodendroglioma
  - Anaplastic oligodendroglioma
- Mixed glioma
  - Oligoastrocytoma
  - Anaplastic oligoastrocytoma
- Embryonal tumors
  - Medulloblastoma
  - Primitive neuroectodermal tumor
- Ependymal tumors
  - Ependymoma
  - Anaplastic ependymoma
  - Myxopapillary ependymoma
  - Subependymoma
- Choroid-plexus tumors
  - Choroid-plexus papilloma
  - Choroid-plexus carcinoma
- Neuronal and mixed neuronal-glioma tumors
  - Gangliocytoma
  - Dysembryoplastic neuroepithelial tumor
  - Ganglioglioma
  - Anaplastic ganglioglioma
  - Central neurocytoma
- Pineal parenchymal tumors
  - Pineocytoma
  - Pineoblastoma

### Histologic Classification of Tumors of the CNS

#### Meningeal tumors

- Meningioma
- Hemangiopericytoma
- Melanocytic tumor
- Hemangioblastoma

#### Primary Central nervous system lymphomas

#### Germ-cell tumors

- Germinoma
- Embryonal carcinoma
- Yolk-sac tumor (endodermal-sinus tumor)
- Choriocarcinoma
- Teratoma
- Mixed-germ cell tumors

#### Tumors of the sellar region

- Pituitary adenoma
- Pituitary carcinoma
- Craniopharyngioma

#### Metastatic tumors

## Distribution of CNS Tumors

- Malignant gliomas, meningiomas, Schwann cell and pituitary tumors are most common primary adult brain tumors
- Benign gliomas, medulloblastomas/PNETs and craniopharyngiomas are most common primary pediatric brain tumors

## Location of CNS Tumors

- Adult
  - cerebral hemispheres
- Pediatric
  - 50% of tumors in children > 1 year of age are infratentorial
  - although majority of tumors in children < 1 year of age are supratentorial, these are chiasmatic-hypothalamic gliomas, medulloblastomas and choroid plexus tumors which are rare in adults

**Are there differences between adult and pediatric non-gliial CNS tumors?**

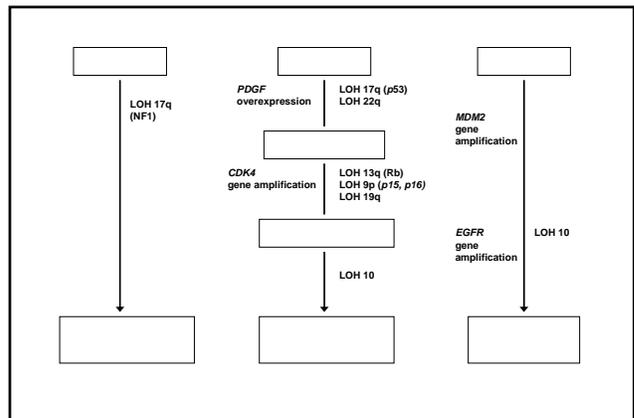
- Neuroepithelial (non-gliial)
- Nerve sheath
- Meningeal
- Germ cell
- Primary CNS lymphoma
- Sellar tumors
- No data supports a meaningful (if any) difference between these tumors in adults and children

**Are there differences between adult and pediatric gliomas?**

- Ependymomas
- Pilocytic astrocytoma
- Oligodendroglioma
- Subependymoma
- Diffuse fibrillary astrocytoma
- No data supports a meaningful (if any) difference between these tumors in adults and children

**Are there differences between adult and pediatric malignant astrocytomas?**

- Anaplastic astrocytoma
- Glioblastoma multiforme



**Are there molecular distinctions between adult and pediatric malignant astrocytoma?**

Compared with adult tumors, + 1p, + 2Q, + 21Q, - 6Q, - 11Q, and - 16Q were more frequent in pediatric malignant glioma.

Rickert et al  
Am J Path 158:1525, 2001

**Are there differences between adult and pediatric malignant astrocytomas?**

Pediatric malignant astrocytoma show preferential p53 pathway inactivation (95%), moderate Rb pathway inactivation (25%), and no EGFR amplification.

Sung et al  
Brain Pathology 10:249, 2000

### **Are there differences between adult and pediatric malignant astrocytomas?**

Peds malignant glioma have moderate rate of p53 mutation (38%), lack of EGFR amplification, a low rate of PTEN mutation (8%), and moderate rate of microsatellite instability (25%).

Cheng et al  
Human Path 30:1284, 1999

### **Are there differences between adult and pediatric malignant astrocytomas?**

Pediatric malignant astrocytomas rarely display EGFR amplification (7%) but frequently display increased EGFR expression (80%).

Bredel et al  
Clin Cancer Res 5:1786, 1999

### **Are there differences between adult and pediatric malignant astrocytomas?**

Malignant astrocytomas in children > 4 years old display TP53 mutations (50%) and p53 overexpression (77%) similar to adult tumors.

Both TP53 mutations (0%) and p53 overexpression (14%) were much lower in children < 4 years of age.

Pollock et al  
Cancer Res 57:304, 1997

### **How do the similarities and differences between adult and pediatric malignant astrocytoma guide the use of the pediatric rule?**

Malignant astrocytomas are more similar than distinct in adults vs. children > 4 years of age

### **Recommendation**

**The Pediatric Rule applies to all adult brain tumors, including malignant astrocytoma**

### **Advantages to joint adult and pediatric malignant gliomas**

- New and improved therapies for our patients
- Better understanding of the underlying biology of these diseases
- Development of common, comprehensive prospective biological studies
- Better understanding of the effects of therapy in both poor and good prognosis groups
- Evolution of new study paradigms
- More efficient study accrual and use of resources

### **Challenges and disadvantages to joint adult and pediatric malignant gliomas**

- Assumptions may be in error and children are exposed to inactive therapy
- Adverse events in children may result in sponsor concerns
- Requirement for cooperation and sharing of resources that may delay or confound study implementation
- Potential need for complex stratification and analysis

## Perspectives on CNS Malignancies

Susan M. Staugaitis, M.D., Ph.D.  
Cleveland Clinic Foundation

## Introduction and Outline

Neoplasia and the Pediatric Rule of 1998  
Evolution in Tumor Classification  
Classification and Incidence of CNS Neoplasms  
Dogma:  
    Indications defined by histology  
Speculation:  
    Indications defined by physiology of neoplastic cell

## Diagnosis of CNS Malignancies – Current Practice and Possibilities

Clinical Diagnosis - Advances in *in vivo* imaging  
    Improved sensitivity clinical diagnosis and disease monitoring  
    Image-guided surgical techniques -  
        Larger resections, but smaller biopsies

Tissue Diagnosis - Role of Pathologist  
Adequacy of specimen  
    Is lesional tissue present?  
    Does the tissue represent the highest grade portion of the lesion?  
    Is there sufficient lesional tissue for all desired analyses?

Classification  
    Histologic phenotype  
    Cytologic grade  
  
    Gene expression  
    Genomic alterations

## Morphologic Classification of CNS Neoplasms

Based upon the cytologic resemblance of neoplastic cells to normal cells  
    Often used to infer cell of origin  
    Become basis of *in vitro* experimental models  
    Doesn't predict the behavior of the neoplastic cells

Site of origin  
    Neoplasms Arising within CNS Parenchyma  
    Neoplasms Arising in Accessory CNS Structures  
    Neoplasms Arising in CNS Coverings

## CNS Parenchymal Neoplasms - "Glial phenotype"

Astrocytoma  
    Fibrillary astrocytoma,  
        including glioblastoma multiforme  
    Pilocytic astrocytoma  
    Pleomorphic xanthoastrocytoma  
Oligodendroglioma  
Ependymoma  
Subependymoma

## CNS Parenchymal Neoplasms - "Neuronal and glial/neuronal Phenotype"

Ganglioglioma/gangliocytoma  
Central neurocytoma  
Dysembryoplastic neuroepithelial tumor  
Desmoplastic infantile astrocytoma/ganglioglioma

## CNS Parenchymal Neoplasms - "Embryonal phenotype"

### Primitive Neuroectodermal Tumors (PNET)

- Medulloblastoma
- Supratentorial PNET/cerebral neuroblastoma
- Atypical teratoid/rhabdoid tumor

## Neoplasms Arising in Accessory CNS structures

- Choroid plexus
  - Papilloma, carcinoma
- Pineal gland
  - Pineal parenchymal neoplasms
  - Germ cell neoplasms
- Pituitary gland
  - Adenoma
  - Neurohypophyseal gliomas/hamartoma
  - Craniopharyngioma

## Neoplasms Arising in CNS Coverings

- Leptomeninges
  - Meningioma
  - Hemangiopericytoma
  - Other sarcomas
  - Melanocytic neoplasms
- Intradural peripheral nerve sheath
  - Schwannoma
  - Neurofibroma

## CNS Neoplasms – Age of Patients Affected

- Adult >> Pediatric
- Pediatric >> Adult
- Pediatric (nearly exclusively)

## Incidence of CNS neoplasms – Adult >> Pediatric

- Most Gliomas
  - Fibrillary Astrocytoma, including GBM
  - Oligodendroglioma
  - Spinal ependymoma
- Pineal Parenchymal Neoplasms
- Meningioma
- Nerve sheath neoplasms
- Melanocytic neoplasms

## Incidence of CNS neoplasms – Pediatric >>Adult

- Low Grade Astrocytomas
  - Pilocytic astrocytoma
  - Pleomorphic xanthoastrocytoma
- Intraventricular Ependymoma
- Neuronal and glial/neuronal neoplasms
  - Ganglioglioma, DNET
- Medulloblastoma
- Choroid Plexus Neoplasms
- Germ Cell Neoplasms
- Craniopharyngioma

## Incidence of CNS neoplasms – Pediatric (nearly exclusively)

Desmoplastic infantile astrocytoma/ganglioglioma  
Atypical teratoid/rhabdoid tumor  
Cerebral PNET

## Pathobiology of Neoplasia

Cell acquire a genetic alteration.  
This alteration results in change in gene expression that provides  
a growth or survival advantage to the cell.  
Genetic alteration is passed onto progeny.  
Additional alterations are acquired and passed on.

## Pathobiology of Neoplasia

Genomic alterations -  
mutation  
rearrangement  
loss or gain of genetic material  
Gene expression -  
intrinsic metabolic pathways  
proliferation, survival, motility  
response to environment  
endogenous signals, drugs

## Pathobiology of Neoplasia

Influence of the precursor cell on the behavior of the neoplasm?  
  
Do different alterations in the same precursor cell result in different neoplasms?  
  
Is there a different precursor for each neoplasm?  
  
Once a precursor cell is transformed by a genetic alteration, does its normal physiologic processes influence the behavior of the neoplasm?

## Pediatric Neoplasms

Some “pediatric” malignancies are low grade and some are high grade.

Time of rapid cell division and growth  
Impact on repair mechanisms?  
Intrinsic versus extrinsic factors  
Cells are proliferating within an environment bathed by growth factors  
What is the role of the environment?  
Does it play an active part in promoting growth in the mature organism?  
Does it play a role in restricting growth in the developing organism?

## Familial Syndromes Associated with CNS Neoplasms

Neurofibromatosis Type 1 - neurofibromin -  
*neurofibroma, pilocytic astrocytoma, fibrillary astrocytoma*  
Neurofibromatosis Type 2 - merlin -  
*schwannoma, meningioma, fibrillary astrocytoma, ependymoma*  
Von Hippel Lindau - VHL - *hemangioblastoma*  
Tuberous Sclerosis Complex - hamartin, tuberlin - *SEGA*  
Li-Fraumeni Syndrome - TP53 - *astrocytoma, medulloblastoma*  
Turcot Syndrome - mismatch repair, APC - *astrocytoma, medulloblastoma*  
Nevoid Basal Cell Carcinoma Syndrome - PTCH - *medulloblastoma*  
Cowden Syndrome - PTEN - *dysplastic gangliocytoma of cerebellum*

## Other ways of characterizing CNS malignancies

### Histopathology perspective

Where do tumors arise? What do they look like?

### Growth properties of the transformed cells

Proliferation/survival

Migration/motility

Angiogenesis

### Growth properties of cell of origin

Can precursor cell be identified?

What are the molecular pathways that regulate the normal phenotype of this cell?

## Rapidly Proliferating Neoplasms - Kill dividing cells

Medulloblastoma

Supratentorial PNET

Atypical teratoid/rhabdoid tumor

Pineoblastoma

High Grade Glioma

Choroid Plexus Carcinoma

## Infiltrating Neoplasms - Inhibit migration

Fibrillary astrocytoma  
Oligodendroglioma

## Angiogenesis

Both high grade astrocytomas and low grade pilocytic astrocytomas show histologically similar vascular proliferation.

Do the same mechanisms promote this proliferation?

If so, can drugs designed to target vasculature in high grade astrocytomas be effective in unresectable pilocytic astrocytomas?

## TP53 mutations

Most common mutation in human cancer

Stimulate p53 function in tumor cells.

If an agents were available, might it be applied to histologically disparate neoplasms?

Inhibit p53 function in normal cells.

Protect normal tissues against genotoxic stress during therapy.

Could this be one indication for all neoplasms with p53 mutations?

## Inhibit function of oncogenic signal transduction pathways

PDGFR-alpha - over expressed in many gliomas

fibrillary astrocytoma

oligodendroglioma

ependymoma

pilocytic astrocytoma

## Inhibit function of oncogenic signal transduction pathways

### EGFR

amplified in de novo glioblastoma  
typically not amplified in glioblastoma that  
arise within low grade astrocytoma

How to define indication?  
Will this limit testing of new drugs?

## Look at entire pathway - not just single component

In a single pathway,  
some genes may acquire  
activating "oncogenic" mutations or  
inactivating "tumor suppressor" mutations.

Both may lead to the same tumor phenotype.

APC + beta-catenin >>  
Wnt pathway

Sonic Hedgehog + Patched + Smoothened >>  
transcription of growth regulating genes

## Cautions

- Necrosis and swelling associated with rapid efficient cell killing may have adverse effects within the confines of the CNS.
- Environmental signals, that may effect the behavior of neoplastic cells, may change during development.
- Specific targeted therapies will work only if the inhibited pathway is intact in the particular tumor being treated.
- Neoplasms accumulate alterations that may lead to specific drug resistance.
- Therapies that target specific functions, e.g., proliferation, migration, may adversely affect normal developing cells that may also depend upon those functions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC SUBCOMMITTEE  
OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

Thursday, June 28, 2001

8:25 a.m.

Advisors and Consultants Conference Room  
5630 Fishers Lane  
Rockville, Maryland

## PARTICIPANTS

Victor M. Santana, M.D., Chairman  
Karen M. Templeton-Somers, Ph.D., Executive  
Secretary

## MEMBER:

Donna Przepiorka, M.D., Ph.D.

## AD HOC MEMBERS:

Susan L. Cohn, M.D.  
Alice Ettinger, MSN, RN, CPON, CPNP  
Jerry Z. Finklestein, M.D.  
Henry S. Friedman, M.D.  
C. Patrick Reynolds, M.D., Ph.D.

## PATIENT ADVOCATES:

Nancy Keen  
Susan L. Weiner, Ph.D.

## CONSULTANTS:

Larry Kun, M.D.  
David M. Parham, M.D.

## GUESTS AND GUEST SPEAKERS:

Robert S. Benjamin,  
Peter Burger, M.D.  
Anthony Elias, M.D.  
Howard A. Fine, M.D.  
Amar Gajjar, M.D.  
Stuart A. Grossman, M.D.  
Frederic Kaye, M.D.  
Victor A. Levin, M.D.  
Michael P. Link, M.D.  
Paul A. Meyers, M.D.  
Roger Packer, M.D.  
Elizabeth J. Perlman, M.D.  
Scott L. Pomeroy, M.D.  
David Poplack, M.D.  
Malcolm Smith, M.D., Ph.D.  
Susan M. Staugaitis, M.D., Ph.D.

## FDA:

Richard Pazdur, M.D.  
Steven Hirschfeld, M.D., Ph.D.  
Joseph Gootenberg, M.D.

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## 1 P R O C E E D I N G S

## 2 Call to Order

3 DR. SANTANA: Good morning. We are  
4 meeting this morning as part of the Pediatric  
5 Subcommittee of the Oncology Drugs Advisory  
6 Committee. This meeting was called by the agency  
7 to give them advice and guidance on issues related  
8 to pediatric development and, in particular,  
9 extrapolation of information from adult studies  
10 that could be relevant to pediatric studies as it  
11 applies to the agency's regulatory role and the  
12 Pediatric Rule.

13 We are going to go ahead and get started.  
14 The first item is to have Dr. Pazdur address the  
15 committee. Richard?

16 Welcome

17 DR. PAZDUR: Thank you very much. This is  
18 one of three meetings that we are having to look at  
19 the 1998 Pediatric Rule which, as Victor alluded  
20 to, allows for the extrapolation of adult data to  
21 the pediatric population. The first meeting looked  
22 at leukemia and lymphomas and, obviously, the  
23 nature of this meeting is looking at other  
24 malignancies, particularly sarcoma, lung and CNS  
25 malignancies and other solid tumors. Our third

1 meeting, which I believe is going to be held in  
2 September, or to be announced -- some of you may be  
3 asked to come back so we will get back to you with  
4 specific dates and your calendars -- will look at  
5 clinical trial design issues in pediatrics to  
6 address issues of extrapolation of data, etc. So,  
7 on behalf of the FDA, our Division of Oncology Drug  
8 Products and our colleagues at CBER who handle  
9 biologics, we would like to welcome you to this  
10 committee meeting and look forward to an ongoing  
11 dialogue with you. Thanks.

12 DR. SANTANA: Thanks, Richard. I want to  
13 go ahead and introduce the committee members.  
14 There are some people that are new to the meeting  
15 and, for the purposes of record-keeping, we need to  
16 state our name and affiliation. So, Stuart, can  
17 you get started from that side of the table please?

18 Introduction of the Committee

19 DR. GROSSMAN: Stuart Grossman, from Johns  
20 Hopkins University.

21 DR. LINK: Michael Link, from Stanford.

22 DR. MEYERS: Paul Meyers from Memorial  
23 Sloan-Kettering.

24 DR. PACKER: Roger Packer, Children's  
25 National Medical Center, Washington, D.C.

1 DR. POMEROY: Scott Pomeroy, Harvard  
2 Medical School.

3 DR. PAZDUR: Richard Pazdur, Oncology  
4 Division, FDA.

5 DR. HIRSCHFELD: Steven Hirschfeld,  
6 Oncology Division, CDER, FDA.

7 DR. GOOTENBERG: Joe Gootenberg, with  
8 Oncology at Biologics, CBER.

9 DR. PARHAM: David Parham, Arkansas  
10 Children's Hospital.

11 DR. KUN: Larry Kun, St. Jude Children's  
12 Research Hospital.

13 DR. COHN: Susan Cohn, Children's Memorial  
14 Hospital in Chicago.

15 DR. ETTINGER: Alice Ettinger, St. Peter's  
16 University Hospital, New Brunswick, New Jersey.

17 DR. FRIEDMAN: Henry Friedman, Duke.

18 DR. TEMPLETON-SOMERS: Karen Somers,  
19 Executive Secretary to the ODAC, FDA.

20 DR. SANTANA: Victor Santana, St. Jude  
21 Children's Research Hospital.

22 DR. FINKLESTEIN: Jerry Finklestein, Long  
23 Beach Memorial, UCLA.

24 DR. PRZEPIORKA: Donna Przepiorka, Baylor,  
25 Houston.

1 DR. REYNOLDS: Patrick Reynolds,  
2 Children's Hospital, Los Angeles.

3 DR. WEINER: I am Susan Weiner. I am the  
4 patient advocate from The Children's Cause.

5 DR. LEVIN: Victor Levin, Department of  
6 Neuro-Oncology, M.D. Anderson Cancer Center.

7 DR. ELIAS: Anthony Elias, University of  
8 Colorado.

9 DR. BENJAMIN: Bob Benjamin, M.D.  
10 Anderson.

11 DR. GAJJAR: Amar Gajjar, St. Jude  
12 Children's Research Hospital.

13 DR. PERLMAN: Elizabeth Perlman, Johns  
14 Hopkins University.

15 DR. POPLACK: David Poplack, Baylor  
16 College of Medicine.

17 DR. SMITH: Malcolm Smith, National Cancer  
18 Institute.

19 DR. STAUGAITIS: Susan Staugaitis,  
20 Cleveland Clinic Foundation.

21 DR. FINE: Howard Fine, Neuro-Oncology  
22 Branch, NIH.

23 DR. SANTANA: That is it. Thank you so  
24 much. We have to read a conflict of interest  
25 statement. So, Karen, can you please proceed with

1 that?

2 Conflict of Interest

3 DR. TEMPLETON-SOMERS: The following  
4 announcement addresses the issue of conflict of  
5 interest with regard to this meeting and is made a  
6 part of the record to preclude even the appearance  
7 of such at this meeting.

8 Since the issues to be discussed by the  
9 subcommittee at this meeting will not have a unique  
10 impact on any particular firm or product but,  
11 rather, may have widespread implications with  
12 respect to an entire class of products, in  
13 accordance with 18 U.S.C. Section 208(b), waivers  
14 have been granted to all members and consultants  
15 who have reported interests in any pharmaceutical  
16 companies.

17 A copy of these waiver statements may be  
18 obtained by submitting a written request to the  
19 FDA's Freedom of Information Office, Room 12A-30 of  
20 the Parklawn Building.

21 With respect to FDA's invited guests,  
22 there are reported affiliations which we believe  
23 should be made public to allow the participants to  
24 objectively evaluate their comments.

25 Victor Levin, M.D., would like to disclose

1 that his retirement fund holds stock in Amgen,  
2 Bristol Myers Squibb, Merck, Alza, Pfizer and  
3 Pharmacia Corporation. Dr. Levin is also the  
4 Program Director of an NIH, NCI National  
5 Cooperative Drug Discovery Group grant,  
6 "Development of Drug Inhibitors of Src" and he is  
7 the Program Director of an NIH, NCI grant "Gliomas:  
8 Biologic, Molecular and Genetic Studies." He is  
9 also on the scientific advisory boards of Direct  
10 Therapeutics, Signase and Oncology Services  
11 Corporation. None of the companies he consults  
12 with have anticancer drugs in clinical trials  
13 except Direct Therapeutics, Inc. Dr. Levin is also  
14 the founder and current member of the Board of  
15 Directors of Signase, Inc. Lastly, his son is  
16 employed by Alza Pharmaceuticals.

17 Susan Staugaitis, M.D. would like to  
18 disclose that she owns stock in American Home  
19 Products, Bristol Myers Squibb and various mutual  
20 funds that may have investments in pharmaceutical  
21 firms.

22 Paul Meyers, M.D. is the principal  
23 investigator on a Bristol Myers Squibb sponsored  
24 Phase I study of Irinotecan in children with  
25 recurrent solid tumor. Dr. Meyers is also a

1 co-investigator for an Ortho-Biotech sponsored  
2 study of erythropoietin in children with solid  
3 tumors. Lastly, he is the principal investigator  
4 on a Genentech sponsored study of Trastuzumab for  
5 recurrent osteosarcoma.

6 Amar Gajjar, M.D. has a grant from  
7 Schering Plough.

8 Anthony Elias, M.D. would like to disclose  
9 that he is a researcher on clinical trials  
10 sponsored by Eli Lilly, Pharmacia and Ribozyme  
11 Pharmaceuticals.

12 Robert Benjamin, M.D. has received  
13 consulting fees from Bristol Myers Squibb, Nexstar  
14 and Sequus. He has also received speaker fees from  
15 Bristol Myers Squibb.

16 Lastly, David Poplack, M.D. would like to  
17 disclose that he has previously received speaker  
18 fees from Chiron and he is an unpaid scientific  
19 advisor to ASTA Corporation.

20 In the event that the discussions involve  
21 any other products or firms not already on the  
22 agenda for which an FDA participant has a financial  
23 interest, the participants are aware of the need to  
24 exclude themselves from such involvement and their  
25 exclusion will be noted for the record.



1 DR. HIRSCHFELD: Thank you, and I want to  
2 thank and commend Dr. Santana for being the  
3 initial, first and unprecedented chair for this  
4 committee and for guiding it through its first  
5 year.

6 DR. SANTANA: And hopefully not the last!

7 DR. HIRSCHFELD: Right!

8 [Slide]

9 Pediatrics has been a driving force for  
10 changes in healthcare and particularly in clinical  
11 investigations. The major regulatory initiatives  
12 of this century were in reaction to  
13 pediatric-driven events. It was the morphine  
14 poisonings in the turn of the 19th to the 20th  
15 century. It was the alfa-nilomide-tainting scandal  
16 which led to the Food, Drug and Cosmetic Act, and  
17 then the amendments to the Food, Drug and Cosmetic  
18 Act which resulted in establishing the three  
19 principles that we use for regulatory science which  
20 is labeling, safety and efficacy which occurred in  
21 1962 as a reaction to the malformations that were  
22 caused by thalidomide.

23 In addition, children have had a key role  
24 in the development of clinical investigations, and  
25 most particularly in oncology. The first

1 chemotherapy studies were done at first in  
2 uncontrolled studies in children and then in  
3 controlled studies. The formation of the National  
4 Cancer Institute and its clinical branches  
5 initially had studies which examined the roles of  
6 chemotherapy and also of statistics and of  
7 randomized controlled study design in children with  
8 leukemia. The advent of adjuvant therapy was first  
9 done in children.

10           Yet, despite all the contributions toward  
11 the development of clinical research and regulatory  
12 efforts, there has never been a robust therapeutic  
13 development program in children. So, there are  
14 some efforts that were initiated over the course of  
15 the last century but most explicitly in the last  
16 decade to try to remedy what many felt was an  
17 unjust situation.

18           We recognize that there are therapies that  
19 were administered to children without adequate  
20 study, both in general and in specific instances  
21 which relate to oncology. We recognize the  
22 extraordinary efforts of the cooperative groups in  
23 developing clinical protocols, and the  
24 extraordinary track record of both enrollment and  
25 of scientific progress. Nevertheless, many of the

1 treatments that are used have been difficult to  
2 come by, and many of the supportive care measures  
3 have never been studied in the types of  
4 environments which we would consider to be ideal,  
5 and we would strive for this ideal. We also note  
6 that many therapies are not made available for  
7 pediatric study until adult marketing studies or at  
8 least the adult program is well under way.

9 [Slide]

10 So, we have here a paradigm where the  
11 conventional and historical method is that  
12 preclinical studies with a new drug or biological  
13 lead to clinical trials in adults, and then  
14 following the adult development sometimes  
15 unintended, sometimes intended, sometimes as an  
16 afterthought comes pediatric development. What we  
17 would like to engender is a new paradigm where  
18 preclinical or non-clinical studies could lead to  
19 either simultaneous adult and pediatric  
20 development, or for those particular instances  
21 where there is an unmet medical need and there is a  
22 scientific basis for proceeding where studies can  
23 lead to therapeutic development in children and  
24 then, if applicable, for adults.

25 These inter-relationships is what we are

1 trying to explore in this committee over the course  
2 of the past year, looking at where we can form a  
3 matrix rather than a linear development plan.

4 [Slide]

5 The FDA, in the 1990's, attempted to  
6 facilitate the availability of drugs for study in  
7 children, and by drugs I mean drugs and  
8 biologicals. With the Rule in 1994 that attempted  
9 to ease the burden of clinical studies by allowing  
10 extrapolation of efficacy data from adult  
11 populations to pediatric populations certain  
12 conditions were met.

13 The conditions were, in brief, that the  
14 indication, which means the disease or condition,  
15 but that the indication is similar in adults and  
16 children and that the mode of action of the  
17 intended therapy is considered similar in adults  
18 and children. Therefore, the burden for scientific  
19 studies would rely on study designs which could  
20 establish appropriate dosing and appropriate safety  
21 information but would not necessarily have to  
22 recapitulate efficacy data.

23 This program was not the success it was  
24 intended to be. So, two other programs were  
25 initiated to replace it. The first was an

1 incentive program, which was part of the 1997 Food  
2 and Drug Administration Modernization Act, which  
3 offered a financial incentive to companies that  
4 were willing to pursue pediatric studies in  
5 response to a written request from the FDA. We  
6 recognize the FDA does not have the resources nor  
7 necessarily the wisdom to know which types of  
8 studies to request so a mechanism was developed to  
9 allow companies or interested third parties to  
10 propose to the FDA pediatric studies, which then  
11 the FDA would evaluate and then amend or issue a  
12 written request on the basis of that proposal.

13           This program has been highly successful.  
14 More pediatric studies have been initiated in the  
15 past five years than ever in the history of  
16 clinical investigations. This program has also  
17 resulted in the issuance of twenty written requests  
18 for pediatric oncology.

19           [Slide]

20           The other regulatory initiative is a  
21 mandate, and the mandate states that if the  
22 indication for an application under review can be  
23 found in children -- and the operative words here  
24 are "indication" and "under review" -- then the FDA  
25 can mandate -- and again the operative word is

1 "can" -- mandate pediatric studies. It applies to  
2 drugs and biologicals. If the indication does not  
3 apply to children or there are other compelling  
4 reasons not to pursue studies in children, then a  
5 waiver can be granted.

6           This rule does not specifically address  
7 the issue of extrapolation of efficacy. What this  
8 rule asks and what I ask this committee to bear in  
9 mind today is are studies warranted. Is there a  
10 scientific basis for considering pediatric studies?

11           I should also note that this rule is not  
12 intended nor has it ever, and we hope ever a  
13 situation would arise where a question comes,  
14 should it delay development for an adult indication  
15 because pediatric studies can always be deferred  
16 and there is no intent to ever delay the  
17 availability or marketing of a new therapy for  
18 adults.

19           [Slide]

20           So, the specific question we would like to  
21 ask the committee this morning and this afternoon  
22 is how should this rule be applied for solid tumors  
23 and central nervous system malignancies.

24           [Slide]

25           What we would hope is that by the end of

1 the day we could have some recommendations for  
2 adult indications that should trigger the Pediatric  
3 Rule; some specific recommendations for adult  
4 indications that should be waived from compliance  
5 with the Pediatric Rule; and when this rule was  
6 written we anticipated the situation, and there are  
7 circumstances such as breast cancer where the  
8 disease does not occur in children or occur in  
9 sufficient numbers that an examination is warranted  
10 every time an application is under review, there is  
11 an automatic waiver. So, our question is should  
12 there be other such conditions?

13 We would like, lastly, recommendations for  
14 general principles that may be used to apply the  
15 Pediatric Rule. We recognize that classification  
16 schema are always changing, are fluid, as they  
17 should be, and rather than convene a committee on a  
18 regular basis to generate lists to update, it would  
19 be helpful and preferable if we could have some  
20 principles articulated to help us apply and  
21 interpret the rule. Thank you.

22 Challenges and Considerations  
23 in Linking Adult and Pediatric Solid Tumors  
24 DR. SANTANA: We will go ahead and do the  
25 presentations and we will have plenty of time for

1 questions and discussion to kind of keep it moving.

2 I am going to go ahead and take the podium.

3 [Slide]

4 What I want to do in the next ten minutes  
5 or so is not to review all the challenges and  
6 indications that may relate to pediatric solid  
7 tumors but actually when I was thinking about doing  
8 this what I decided to do were two things. One is  
9 to kind of give a general overview consensus of  
10 what I have taken out of the past couple of  
11 discussions of this committee and my understanding  
12 of where pediatric research and FDA regulatory  
13 issues converge. Then, lastly, I would like to  
14 bring forth the two points that to me are critical  
15 as we move forward in considering extrapolation of  
16 data, the two questions that we should always ask  
17 when we are faced with that challenge. So,  
18 hopefully, in the next ten minutes I will be able  
19 to cover all that.

20 [Slide]

21 Clearly, there are two major issues here.  
22 One is the research implications and the other one  
23 is the regulatory implications, and by regulatory  
24 implications I am only focusing on the FDA  
25 perspective as it relates to the Pediatric Rule.

1 [Slide]

2 I think these are really a continuum, and  
3 I think in pediatrics, and particularly in  
4 pediatric oncology, we have a major advantage in  
5 that pediatric oncology practice really occurs  
6 almost exclusively within the research setting and  
7 research trials are really the standard of care for  
8 children in the United States who have cancer.  
9 This is in real contrast to what happens in adult  
10 oncology in which this is not the case or what may  
11 happen in other pediatric diseases that are not  
12 oncology in which research trials are not the  
13 primary driving force of how patients are taken  
14 care of.

15 From the regulatory perspective, once  
16 again just focusing on the comment of how it  
17 relates to the FDA and the Pediatric Rule, I think  
18 we have to remember that the FDA is always looking  
19 and the sponsors are always presenting data to the  
20 agency in support of indications. I mean, that is  
21 the ultimate goal of why they come to the agency.  
22 In support of indications, obviously, they are  
23 interested in looking at issues of efficacy as an  
24 important endpoint but, as Steven addressed a  
25 little bit earlier, a major component relates to

1 issues of safety and most of the mishaps that have  
2 occurred in pediatric regulatory issues have  
3 actually been issues related to safety and I am  
4 going to talk a little bit about that later in  
5 regards to some of the oncology drugs and how we  
6 may address those.

7 I think whatever sponsors and the FDA do  
8 with indications ultimately influences medical  
9 practice not only in adults but also to a certain  
10 degree in pediatrics, although in pediatric  
11 oncology the ongoing theme is always that it is  
12 done in the setting of research.

13 [Slide]

14 Now, I think we have to recognize that  
15 there are some major limitations in pediatrics.  
16 One is that we have a limited patient population.  
17 So, many of the questions that we would like to  
18 address many times cannot be addressed because  
19 there is a limiting factor in terms of the number  
20 of patients. A corollary to that is that many of  
21 the diseases and solid tumors, for example, that we  
22 treat are very heterogeneous in nature and there  
23 are not large populations of patients within one  
24 tumor category in which we can ask many different  
25 questions. So, this is very different if you look

1 at it from the adult perspective because from the  
2 adult perspective, in terms of drug development,  
3 there are many agents that can be tested in a Phase  
4 I setting because there are many adults in terms of  
5 the numbers that can help us address those  
6 questions.

7           Secondly, there are even fewer new agents  
8 that can be evaluated in Phase II trials in  
9 children because of the historical notion that many  
10 trials first had to be conducted in adults before  
11 any studies could be conducted in children. As  
12 Malcolm Smith has reminded us many times, for many  
13 of the pediatric solid tumors we can realistically  
14 only do a Phase III study every four or five years  
15 because of the issues of number of patients and the  
16 issues of which are the real important questions  
17 that have to be answered. I think the example  
18 there is what has happened with Ewing's sarcoma and  
19 osteosarcoma in the last decade in which  
20 realistically, at the national level, Phase III  
21 studies in those tumor types could only be carried  
22 on in the context of every four to five years. I  
23 think that is important as, from the research  
24 perspective, we try to address what are the real  
25 questions that we should be asking.

1                   So, from the research perspective there  
2 need to be mechanisms by which we can prioritize  
3 what we can do in pediatric oncology with our  
4 trials, and I think these three points that Malcolm  
5 Smith has expressed before are that these  
6 prioritizations have to be based on some idea of a  
7 successful approach in adults because of the issue  
8 of the limitation of patient numbers; that there be  
9 compelling preclinical rationales for why these  
10 questions with these agents should be asked in  
11 children; and then paying some close attention to  
12 the patient population at hand because there may be  
13 specific patient populations in pediatric oncology  
14 in which this may be more reasonable. For example,  
15 patients at high risk for recurrence provide a  
16 unique mechanism for us to be able to ask some of  
17 these research questions.

18                   [Slide]

19                   However, as Steven addressed this a little  
20 bit earlier, one of the primary concerns always in  
21 pediatric research is this issue that we have to  
22 obtain useful data. It is going to be limited  
23 data, and a central issue is always the issue of  
24 safety in children. None of us wants to be  
25 involved with issues in which an agent, even in a

1 research setting or a regulatory setting, has had  
2 children involved and major mishaps occur. I think  
3 it not only presents issues of our relationship  
4 with the community but also from an ethical point.  
5 We want to make sure that what we do with children  
6 is always safe.

7           So, I think we have to recognize that  
8 there always have to be studies done in children  
9 with new agents to help us understand whether the  
10 MTD, the pharmacokinetics and the pharmacodynamics  
11 are truly different so that when these agents then  
12 become publicly available we don't have issues with  
13 safety.

14           The two that I have outlined here are good  
15 examples. As you know, Taxol is not a drug that we  
16 use a lot in solid tumors or in pediatric oncology,  
17 but the schedules of administration of Taxol are  
18 really very different in adults versus children,  
19 and that relates primarily to the vehicles in which  
20 this drug was originally formulated and the  
21 toxicity that the vehicle may present when it is  
22 given to children in very short infusions.

23           Similarly, teniposide, where the vehicle  
24 preparation has a lot of alcohol in it, one has to  
25 be very careful with high doses of teniposide in

1 children because potentially issues of alcohol  
2 toxicity may be related to the safety in use of  
3 this drug.

4           So, the point here is just to present to  
5 you two very brief examples of how we cannot  
6 technically extrapolate all the adult data in terms  
7 of pharmacokinetics and dynamics to children  
8 because there may be particular issues with  
9 children that have to be addressed in the safety  
10 issue.

11           Then, lastly -- I don't want to beleaguer  
12 this point of safety but we have to recognize that  
13 there are different populations and even babies are  
14 different from ten-year olds and fifteen-year olds  
15 as relates to the metabolism of drugs.

16           [Slide]

17           So, the question that we have for us today  
18 that Steven presented, under the auspices of this  
19 Pediatric Rule, how do we consider whether solid  
20 tumors in adults and children are either similar or  
21 different, and why is it important to us and why  
22 are we here?

23           Well, I think the first point is that  
24 there are truly limited opportunities to test new  
25 agents in children so we have to be very careful in

1 what we bring forward.

2           We have to make this regulatory mandate  
3 very practical. I think Steven was hinting at  
4 that. We have to be careful that, from our  
5 business partners in the pharmaceutical industry,  
6 that we don't ask them to do things that are  
7 unrealistic and impractical. We have to make this  
8 mandate very practical for the benefit of us in the  
9 research community, for the benefit of our  
10 patients, and certainly for the benefit of the  
11 industry. This has to be done in a very practical  
12 way to make these agents then available for  
13 children.

14           I think you are going to hear a little bit  
15 of discussion today from various other presenters  
16 about ways in which potentially we can address this  
17 question of extrapolation of data by looking at  
18 phenotype. I am a believer that an osteosarcoma in  
19 a 10-year old is the same thing as an osteosarcoma  
20 in a 25-year old. Maybe somebody believes  
21 differently. We will hear that maybe today.

22           We could look at it from the genotypic  
23 point of view, from the molecular point of view.  
24 There may be common genotypes or molecular events  
25 that make us believe that tumors are very similar

1 although histologically they may be very different.

2 [Slide]

3 So, my two rules then in trying to answer  
4 this question are what two things am I going to be  
5 looking for to help me decide whether things are  
6 different or are similar enough that I could  
7 consider them the same? I think in that regard the  
8 two points that I hope we will hear some discussion  
9 today of are, first of all, looking at the biology,  
10 are there differences and similarities in the  
11 biology? That is, what creates the disease  
12 phenotype? If that is similar enough, are we  
13 really talking about the same disease and the same  
14 manifestations?

15 The second point is that as we try to  
16 extrapolate data we need to look at the host, and  
17 we need to look at differences and similarities in  
18 the host because that may be critical in terms of  
19 determining drug metabolism and toxicity and  
20 relating to issues of safety, which is obviously a  
21 primary concern.

22 [Slide]

23 Lastly, I want to present to you kind of a  
24 general outline of how we may consider some of  
25 these points in terms of extrapolating both the

1 biology and in terms of extrapolating host factors.  
2 The progression and the malignant transformation  
3 for the same tumor type may be very similar or may  
4 be very different in children versus adults. There  
5 may be common elements, such as drug resistance,  
6 that tell us that the disease clinically behaves  
7 the same way. Or, there may be differences in host  
8 factors and enzyme polymorphisms that may lead us  
9 to believe that, from the safety perspective, this  
10 is an issue that we need to address in a different  
11 population by looking at different pediatric  
12 populations in a very unique way.

13           So, I wanted to finish here by just giving  
14 you my perspective on this issue in a very general  
15 sense. My intent was not to discuss every single  
16 solid tumor and the challenges and implications of  
17 that because I think that will be done later today  
18 by other speakers. Thank you. Henry?

19                           Challenges and Considerations  
20           in Linking Adult and Pediatric CNS Malignancies

21           DR. FRIEDMAN: This is a special day for  
22 me since I have never done power-point before and I  
23 want someone to come up and show me something, and  
24 to be sure this went well I sent the slides ahead  
25 to Karen and to Steve, the FDA, living and dead,

1 Congress and the District of Columbia. So, there  
2 are a lot of slides that are out there.

3 [Laughter]

4 DR. SANTANA: Remember, Henry, that  
5 everything you say here will be in the public  
6 record. Okay?

7 DR. FRIEDMAN: I always remember that! I  
8 strive for that!

9 [Slide]

10 What I am going to try to do today is to  
11 show some of the challenges and considerations  
12 involved in linking adult and pediatric CNS tumors.

13 [Slide]

14 The question posed is what is the  
15 relationship between adult and pediatric CNS  
16 tumors? Are there compelling similarities or  
17 differences in these tumors which can guide us in  
18 the application of the Pediatric Rule of 1998?

19 [Slide]

20 This shows you the histologic  
21 classification of tumors of the CNS taken from the  
22 most recent WHO publication. You can see that  
23 tumors are divided into neuroepithelial tissues,  
24 astrocytic, oligodendroglial, mixed glioma and  
25 embryonal, ependymal, choroid-plexus, neuronal and

1 mixed neuronal tumors and pineal parenchymal tumors

2 --

3 [Slide]

4 -- continuing with meningeal tumors,  
5 primary CNS lymphomas, germ cell, tumors of the  
6 sellar region and metastatic tumors. So, the real  
7 question is what is the difference in the adult and  
8 pediatric population?

9 [Slide]

10 First off, malignant gliomas, meningiomas,  
11 Schwann cell and pituitary tumors are the most  
12 common tumors we see in the adult population as  
13 opposed to benign gliomas, medulloblastomas/PNETs,  
14 which is primitive neuroepidermal tumor, and  
15 craniopharyngiomas which are the most common in the  
16 pediatric population.

17 [Slide]

18 The vast majority of adult tumors are in  
19 the cerebral hemispheres. In pediatrics more than  
20 50 percent of tumors in children who are over a  
21 year in age are infratentorial, but a majority of  
22 tumors in children less than one year of age are  
23 also supratentorial but they are different from the  
24 adult tumors -- the chiasmatic-hypothalamic gliomas  
25 and choroid plexus tumors.

1 [Slide]

2 So, are there differences between adult and  
3 pediatric non-glial CNS tumors -- the  
4 neuroepithelial, nerve sheath, meningeal, germ  
5 cell, CNS lymphoma, sellar tumors? The bottom line  
6 is that there is no compelling data which suggests  
7 that there is a meaningful difference between these  
8 tumors in adults and children. There may be  
9 differences but at the biological level there is no  
10 compelling data to say there is a difference.

11 [Slide]

12 Are there differences between adult and  
13 pediatric gliomas -- ependymomas, pilocytic  
14 astrocytoma, oligodendroglioma, subependymoma,  
15 diffuse fibrillary astrocytoma? Again, no data  
16 supports a meaningful, if any, difference between  
17 these tumors in adults and children. I want to  
18 acknowledge Peter Burger's help in looking at some  
19 of these issues. He was very helpful in our  
20 discussions.

21 [Slide]

22 So, we really resolve to are there  
23 differences between adult and pediatric malignant  
24 astrocytomas -- the anaplastic astrocytomas, the  
25 glioblastoma multiforme?

1 [Slide]

2 This is taken from a number of different  
3 sources, one of David Lewis' publications most  
4 recently, showing you a number of the molecular  
5 changes that occur in the development of a  
6 pilocytic astrocytoma, the so-called secondary  
7 glioblastoma multiforme and the primary  
8 glioblastoma multiforme which has a hallmark of  
9 EGFR gene amplification. But, again, how does this  
10 help us with pediatric versus adult? You have  
11 copies of all these slides.

12 [Slide]

13 So, a series of questions, the same  
14 question slide after slide now: are there molecular  
15 distinctions between adult and pediatric malignant  
16 astrocytoma? Rickert et al., in American Journal  
17 of Pathology, 2001, compared adult tumors. Plus  
18 1P, plus 2Q, plus 21Q, minus 6Q, minus 11Q, and  
19 minus 16Q were more frequent in pediatric malignant  
20 glioma than in adult malignant glioma.

21 [Slide]

22 Sung, et al., in Brain Pathology, 2000,  
23 pediatric malignant astrocytoma show a preferential  
24 p53 pathway inactivation, 95 percent or more,  
25 moderate RB pathway inactivation, 25 percent, and

1 no EGFR amplification.

2 [Slide]

3 Cheng, in Human Pathology, '99, pediatric  
4 malignant gliomas have moderate rates of p53  
5 mutation, a lack of EGFR amplification, a low rate  
6 of PTEN mutation, and a moderate rate of  
7 microsatellite instability as opposed to adult  
8 tumors.

9 [Slide]

10 Pediatric malignant astrocytomas rarely  
11 display EGFR amplification but frequently display  
12 increased EGFR expression, from Bredel, et al., in  
13 Clinical Cancer Research.

14 [Slide]

15 Pollock showed malignant astrocytomas in  
16 children greater than four years of age display  
17 TP53 mutations and p53 overexpression similar to  
18 adult tumors. Both TP53 mutations and p53  
19 overexpression were much lower in children less  
20 than four years of age, showing a difference in the  
21 true biology of older and younger children.

22 [Slide]

23 Again, malignant astrocytomas are more  
24 similar than distinct in adults versus children  
25 greater than four years of age. So, in the older

1 child, although there are obviously distinctions in  
2 their molecular phenotype or molecular expression  
3 of genes, the similarities are greater than the  
4 distinctions.

5 [Slide]

6 I would like to modify this slide a bit.  
7 The Pediatric Rule applies to all adult brain  
8 tumors, including malignant astrocytoma, however,  
9 as we have started to hear and will continue to  
10 hear, the number of tumors in pediatrics -- the  
11 resources are so limited that it is going to be key  
12 that there not be just a reflex application of the  
13 Pediatric Rule to any adult brain tumor, but that a  
14 discussion with the representative groups that are  
15 addressing this problem be held on a tumor by tumor  
16 or trial by trial basis to make a decision whether  
17 it is appropriate to actually extend the rule and  
18 enforce it.

19 [Slide]

20 Advantages -- and I want to thank Steve  
21 Hirschfeld for help with this -- to joint adult and  
22 pediatric malignant gliomas, new and improved  
23 therapies for the patients; a better understanding  
24 of the biology of the diseases; development of  
25 common, comprehensive prospective biological

1 studies; a better understanding of the effects of  
2 therapy in poor and good prognosis groups; new  
3 study paradigms; more efficient study accrual and  
4 use of resources.

5 [Slide]

6 However, we may be making some assumptions  
7 that are in error in children exposed to therapies  
8 of no merit. There is always the concern of  
9 adverse events in children having a greater pebble  
10 in the pond effect than in the adult population --  
11 just intrinsically the way this country operates.  
12 Requirement for cooperation and sharing of  
13 resources may delay or confound study  
14 implementation. I think the merger of POD and CCG  
15 has formed one central organization. There is also  
16 the Pediatric Brain Tumor Consortium. More groups  
17 mean more committees; more committees means more  
18 time, not necessarily time well spent. Potential  
19 need for complex stratification and analysis.

20 But the bottom line is that we have an  
21 opportunity when the situation is appropriate to  
22 take advantage of the Pediatric Rule because I  
23 don't believe, and we will see how the discussion  
24 goes today, that we will see a situation where we  
25 want to apply the rule and we don't have grounds to

1 apply the rule. Thank you.

2 Discussion

3 DR. SANTANA: Thanks, Henry. We now have  
4 time for discussion of the three prior speakers if  
5 anybody has any questions to Steven, to Henry or  
6 myself or want to make any general comments about  
7 where we are so far. Paul?

8 DR. MEYERS: Henry, I think you made a  
9 very compelling case that the biology is strongly  
10 in favor of linking the pediatric and adult brain  
11 tumors, but you didn't address the issue of  
12 toxicity and whether or not you think there are  
13 specific toxicities for brain tumor treatment that  
14 would impede that ability.

15 The other question I would like to ask you  
16 is are there any clinical differences in the  
17 behavior of these tumors? I recognize we should  
18 all be looking at biology as the more fundamental  
19 question but, for example, do these tumors progress  
20 more rapidly in children and does that have an  
21 implication for clinical trial design?

22 DR. FRIEDMAN: In terms of the second  
23 question first, I don't know how to answer that  
24 because therapies are so distinct that the clinical  
25 course of the tumors is obviously going to be

1 influenced by the interventions you use, and the  
2 approaches in the adult and the pediatric  
3 population are frequently quite disparate. So, it  
4 is hard to answer that question. I will turn it  
5 over to others -- Roger perhaps -- in a second.

6           The first question, certainly, I think the  
7 toxicities are going to be an issue. If there is  
8 going to be an adult trial which is going to use  
9 50,000 sonograde whole brain radiotherapy, perhaps  
10 in pediatrics we might frown upon that kind of a  
11 study. I am only kidding, folks; we are not going  
12 to do that. But, certainly, there are going to be  
13 situations where, because of the developing CNS, we  
14 might be eager to avoid certain interventions.

15           If you are talking about things that have  
16 unclear neurotoxicity, that will have to be  
17 factored in. I mean, certainly if there are  
18 interventions which you know are going to pose more  
19 risk of damage and you know you have a more  
20 vulnerable situation in the pediatric population,  
21 you are going to have to think about it. That is  
22 part of the rationale for a case by case type of  
23 situation, or tumor by tumor.

24           DR. MEYERS: I guess what I am suggesting  
25 is that Steve was looking to us to try to draw

1 general principles, and I am almost hearing from  
2 you that you think that is unlikely to be a  
3 possibility. You are really suggesting that we are  
4 going to need to look at each of these agents  
5 individually.

6 DR. FRIEDMAN: Correct, absolutely  
7 correct. Roger?

8 DR. PACKER: I really want to comment  
9 mainly on the second point. I think that one of  
10 the mistakes potentially made is that there has  
11 been a tremendous reservation to look at new agents  
12 in pediatric brain tumors because of the potential  
13 effects on the developing nervous system. There  
14 are ways now to monitor those effects, to evaluate  
15 them. There are certainly tumors for which we have  
16 really very little to offer patients. We are  
17 really hung up often by not being able to look at  
18 those agents. If we monitor them appropriately --  
19 we have MRI; we have neuro-cognitive assessments;  
20 we have ways to monitor toxicity -- it shouldn't be  
21 the rate limiter to applying the rule, there may  
22 just have to be better considerations for how you  
23 evaluate toxicity.

24 The other component of that is that it is  
25 a true marketing issue for many of the companies.

1 If they get into a toxicity that may delay the drug  
2 getting to market, that is the major limitation.  
3 And, as we are looking at the new drugs we are not  
4 only looking at chemotherapies, we are looking at  
5 biologics, we don't know how turning on and off  
6 these genes is going to affect the development of  
7 the nervous system. We are looking at new drug  
8 delivery methods -- convection delivery for CNS  
9 tumors, and we are worried about the volume of the  
10 brain. There is always this tremendous difficulty  
11 to get over the barrier as we work with new  
12 companies, pharmaceutical firms, etc., of trying to  
13 get them to apply these to pediatrics.

14 I don't have the answer, except I think  
15 sometimes it is overblown where the damage is going  
16 to be. If there is going to be damage it will  
17 identify it if we choose the target population  
18 appropriately in those children who have no other  
19 options, which is where I think these things should  
20 be started, then I think the issue of CNS damage,  
21 though an important one, is often a secondary one.

22 DR. ELIAS: I just have a comment on  
23 something Victor said, and that is that basically  
24 we are talking really about Phase II/Phase III type  
25 of indications. It is clear from your discussion

1 that Phase I cannot be bypassed. The pediatric  
2 populations are sufficiently different in a variety  
3 of way the PK, growth of the organism, and so forth  
4 -- that you really cannot bypass the safety  
5 considerations. But what we are really talking  
6 about in terms of the Pediatric Rule, I believe,  
7 would be the Phase II/III indications for market  
8 basically.

9           But I also agree that the safety issues  
10 represent a major stumbling block in terms of  
11 developing drugs, new agents. None of the  
12 pharmaceutical companies want toxicities associated  
13 with their agent.

14           DR. HIRSCHFELD: I will make a comment,  
15 and these are just general comments, and I will  
16 also invite Dr. Pazdur to follow up if he wishes.  
17 But I cannot think of a single example of the  
18 85-plus drugs that we have approved where toxicity  
19 has proved to be the stumbling block. It is always  
20 the issue of potential benefit versus potential  
21 risk. I think it is clear that we have put an  
22 enormous number of highly toxic substances out on  
23 the market -- not us per se, I mean the  
24 pharmaceutical industry and the academic  
25 investigators and everyone, but we have allowed

1 these products to be on the market despite, in some  
2 cases, their substantial toxicities because there  
3 is a perceived benefit that, at least based on the  
4 available data, seems to outweigh the potential  
5 risks. It is one of the reasons why there are  
6 medical oncologists and pediatric oncologists,  
7 because we require that there be physicians and  
8 facilities which specialize in the treatment and  
9 monitoring of the patients in order to administer  
10 these therapies.

11           The other issue that I wanted to comment  
12 on in terms of general points is that while we may  
13 not have specific principles, I think that if we  
14 would look for patterns, and I think by the end of  
15 the day we may see some emerge, we should keep our  
16 minds open as to what potentially may evolve. Dr.  
17 Pazdur, did you want to comment?

18           DR. PAZDUR: Basically, if you take a look  
19 at why NDAs do not get approved, it is not because  
20 of toxicity but because of lack of efficacy, by and  
21 large. The toxicity issues are usually answered  
22 well in advance to the time they get into an NDA  
23 situation as far as major toxicities. Unusual  
24 toxicities, especially if they occur in a pediatric  
25 population, could be handled in labeling

1 considerations or in further studies.

2           But this kind of fear that the FDA will  
3 halt the development of a drug because we see an  
4 unusual toxicity in a subpopulation I think may be  
5 somewhat overblown. Yes, we are interested in the  
6 toxicity. It may require further studies, but a  
7 lot of that could be handled in labeling issues or  
8 in really looking at the toxicities in  
9 subpopulations. The major issue of approval or  
10 non-approval of NDAs is not toxicity; it is the  
11 lack of efficacy, and I think a sponsor should be  
12 well aware of that.

13           DR. FINE: I think the only caveat I would  
14 say in speaking about brain tumors in particular,  
15 and later on in the afternoon I am going to address  
16 some of the clinical differences between the  
17 pediatric brain tumors and adult brain tumors, but  
18 I think it is important to say that efficacy can be  
19 defined, obviously, in very many different ways and  
20 particularly for adult brain tumors, where we are  
21 dealing mostly with malignant gliomas where the  
22 prognosis is so poor and our therapeutic  
23 interventions are so limited, we are more likely to  
24 approve a drug with marginal benefit and with  
25 issues of long-term toxicity hardly being an issue.

1           However, taking pediatric tumors as a  
2 whole, and we will talk about the specifics as the  
3 day goes on, generally, thank God, children tend to  
4 do better as a whole than the adults, maybe not per  
5 high grade tumor but as a whole. So, for a  
6 marginal benefit, if there is some significant  
7 long-term toxicity we may be more reticent to  
8 approve that drug for a pediatric indication than  
9 for an adult. I think that is the one caveat I  
10 would say.

11           DR. FINKLESTEIN: I think our challenge is  
12 to think out of the box, and thinking out of the  
13 box and going back to the history probably of the  
14 generation of this committee, the idea was how can  
15 we bring new ideas, new agents, new drugs to the  
16 pediatric population earlier so the lag time would  
17 be shortened? Dr. Hirschfeld referred to that in  
18 terms of the algorithms that he was showing.

19           So, I would prefer that we not discuss or  
20 not use the phrase we are only considering Phase  
21 II/Phase III studies. What we are considering and  
22 what our challenge is, as I understand it, is  
23 bringing the pediatric oncologic challenge to the  
24 forefront and thinking of a different way of  
25 getting our children to have an opportunity to get

1 new agents earlier on, and the contributions of  
2 Henry are excellent because by thinking together in  
3 a unison manner in terms of brain tumors this will  
4 help us. Now, I understand there have to be some  
5 exceptions, but I would really hope we will think  
6 out of the box and not think of the old algorithm  
7 because that is what we really want to get away  
8 from.

9 DR. PRZEPIORKA: A question for Steven.  
10 Victor and Henry both highlighted the fact that  
11 these tumors are not real prevalent in the  
12 pediatric population. Can you bring us up to date  
13 on what the FDA is doing to logistically identify  
14 the priorities within the pediatric oncology  
15 community for drugs in pediatric solid tumors and  
16 CNS malignancies?

17 DR. SANTANA: Maybe Malcolm will want to  
18 comment.

19 DR. HIRSCHFELD: I will refer to Malcolm  
20 but I will start by saying we wish we were in the  
21 position of having to prioritize these, but we are  
22 not. So, we are looking prospectively and  
23 hopefully at the circumstances.

24 I will just make one more point and then I  
25 will ask Dr. Malcolm Smith, who has taken a

1 leadership role in this arena, to address your  
2 question in more detail. But the other general  
3 point is that the '98 rule mandates that the drug  
4 be made available for studies, or the biological.  
5 It doesn't say it should be approved for children.  
6 It doesn't say that it should be in any other way  
7 disseminated but should be in a controlled  
8 circumstance, made available for studies, and that  
9 was the principle I wanted to emphasize. Can I  
10 just turn it over to Dr. Smith?

11 DR. SMITH: I would emphasize some of what  
12 Victor said, that there is the need for  
13 prioritization. In terms of the prioritization  
14 process, I think it needs to lay with the experts  
15 in the pediatric cancers. So, we are trying to  
16 facilitate the prioritization process through the  
17 Children's Oncology Group and its Phase I  
18 Consortium; through the Pediatric Brain Tumor  
19 Consortium; through the disease committees of the  
20 Children's Oncology Group. We think that is where  
21 the prioritization needs to occur.

22 The kind of tools for prioritization --  
23 and again Victor mentioned some of these, you know,  
24 if an agent looks super in an adult carcinoma maybe  
25 it is good in a pediatric embryonal tumor. It is a

1 good question. But we are trying to develop ways  
2 for prioritizing better, having additional data to  
3 base some of these decisions about whether the best  
4 drug for rhabdomyosarcoma is going to be a  
5 rhabdomyocin analog or protease inhibitor or an  
6 epidermal growth factor, etc., inhibitor or, you  
7 know, SDI571, all of which are either in the clinic  
8 in pediatrics or soon will be. So, we get to the  
9 point Victor was making, how many of those will we  
10 be able to study in Phase II in rhabdomyosarcoma or  
11 osteosarcoma? Then, which of those will we select  
12 to be our Phase III drug for the next four or five  
13 years, the question of therapy that we are asking?

14           We are trying to work with the pediatric  
15 research community to develop additional ways of  
16 using preclinical data to inform those decisions.  
17 We sponsored a meeting together with the Children's  
18 Oncology Group Phase I Consortium yesterday to  
19 begin assessing what tools there are available now  
20 for preclinical models, and then how those tools  
21 might be used in a more systematic way. I think  
22 that will be a key component to the prioritization  
23 process, and making more information available to  
24 the people making the decisions in the Phase I  
25 Consortium, the Brain Tumor Consortium, the disease

1 committees within COG.

2 DR. SANTANA: I want to take the  
3 chairman's prerogative and ask anybody in the  
4 audience from the pharmaceutical industry who wants  
5 to comment on these issues, because I think we are  
6 having a discussion here from the academic centers  
7 and from the regulatory agencies but the third  
8 point here in the triad is the business and  
9 pharmaceutical. So, I know there are a couple of  
10 representatives here and so I would invite anyone  
11 from the industry who is here who wants to comment  
12 on this particular issue to come to the podium.  
13 Please take the invitation. You don't get many  
14 opportunities. I will give you a couple of minutes  
15 to get your thoughts together.

16 DR. HIRSCHFELD: I just want to make one  
17 other clarifying comment on the general principles,  
18 and this applies to both the Pediatric Exclusivity  
19 Initiative and the Pediatric Rule. What we are  
20 attempting to facilitate is the generation of  
21 information, data, as it relates to pediatrics.  
22 So, in the Pediatric Exclusivity program we are  
23 willing to give a financial incentive for even  
24 negative data because we consider it important that  
25 there be credible data available for study in

1 children. The same with the Pediatric Rule, even  
2 if the drug does not lead to approval or leads to  
3 an indication, it will still provide useful data.

4           The mechanism that we have for  
5 disseminating the useful data is in the product  
6 label, and we would consider it an effort well  
7 worth the undertaking if we were able to write  
8 information which was of use to practitioners in a  
9 product label, again, even if it didn't lead to an  
10 indication.

11           DR. SANTANA: Roger?

12           DR. PACKER: A comment and then a question  
13 to the committee. The comment is I am not  
14 absolutely sure that prioritization is not an  
15 issue. We have already run into the road blocks in  
16 some of the new angiogenesis and biology drugs of  
17 how we are going to prioritize those drugs and how  
18 we are going to apply them to pediatrics. We have  
19 also hit road blocks at the regulatory level, at  
20 the government regulatory level of allowing those  
21 drugs to go into pediatric trials for pediatric  
22 brain tumors until there is some adult data showing  
23 their efficacy, which is a real problem in some of  
24 the things. I don't want to go into specifics but  
25 just to say that at the regulatory level it isn't

1 all that black and white, that there are road  
2 blocks at this point.

3           The question to the committee though is  
4 that I understand, I think, fairly well how this  
5 rule is applied in one direction and it hasn't been  
6 that difficult for many of the investigators here  
7 to take a drug in adult malignant gliomas and apply  
8 it to pediatric malignant gliomas. I think the  
9 drug companies understand that the regulatory  
10 agencies understand it. Where I have difficulty is  
11 how is this drug or biologic going to be applied  
12 for tumors where there is not a tremendous interest  
13 in adult trials? How are we going to apply it  
14 where there aren't drug trials for low grade  
15 gliomas, which is a major pediatric problem?  
16 Whether or not drug trials for primitive  
17 neuroectodermal tumors in adults, which is a major  
18 pediatric problem -- what data will be utilized by  
19 the FDA to make this rule apply to those tumors  
20 that are not in trials in adults?

21           DR. LEVIN: I would like to expand on that  
22 just a bit and clarify one aspect of it, and that  
23 is that the same problems exist in the adult groups  
24 for treating anaplastic astrocytomas because  
25 getting access to new drugs is basically focused on

1 the fast market approach of looking at glioblastoma  
2 and for many of these new drugs that is not the  
3 target. The target is a much lower grade tumor.  
4 So, we have the same problems that you do in  
5 addressing anaplastic tumors and lower grade  
6 astrocytic tumors.

7 I would like to make one more comment and  
8 maybe put it in a different light, and that is  
9 basically for the less common tumors what you are  
10 really all talking about is developing at a  
11 preclinical level target identification which would  
12 justify the use of a pharmaceutical agent that will  
13 be coming out. And, I think the goal should be to  
14 get access to a drug irrespective of whether there  
15 is an adult counterpart, but basing the access of  
16 the drug on the need to address inhibition of a  
17 target.

18 I think that that approach needs to be  
19 utilized, but I would agree it is hard to imagine  
20 that the pharmaceutical industry would be willing  
21 to give you a drug that is, say, used in small cell  
22 or being developed for small cell carcinoma and you  
23 are going to mount a trial now in medulloblastoma  
24 where you are basically going to have to do Phase  
25 I, Phase II and everything. That probably should

1 be one of the major goals of this committee, to try  
2 to work out a way that makes it easier, maybe gives  
3 the pharmaceutical company some either regulatory  
4 or financial incentive to let that drug out for the  
5 use in pediatrics.

6 DR. PAZDUR: That is the whole pediatric  
7 plan that we developed under the FDAMA  
8 interpretation, our interpretation of FDAMA, which  
9 allows the development of drugs in the pediatric  
10 population in a Phase I population, and even if  
11 there is prohibitive toxicity, if there is a good  
12 faith attempt that a Phase I study is done, then  
13 they get the carrot of six months exclusivity  
14 attached to their entire product line. Likewise,  
15 if they do a Phase II study and it turns out  
16 negative, it is a good faith attempt in providing  
17 what we require as needed information so they do  
18 get that carrot. So, that has been built into the  
19 exclusivity plan for the development of pediatric  
20 drugs.

21 DR. SANTANA: Steven?

22 DR. HIRSCHFELD: Yes, I wanted to just  
23 address the matrix issue once more. Rather than  
24 necessarily thinking of a triad of investigators,  
25 regulators and industry, I want to emphasize a

1 matrix. And, there are many other components, most  
2 important patients and their families because they  
3 are the ones who are the focus of all our efforts,  
4 and many other people who have an interest in it.  
5 I think that we have made an attempt to engage in  
6 dialogue with as many people as we think have an  
7 interest or, as they are called fashionably these  
8 days, stakeholders in the problem, and I think it  
9 will require efforts which will involve all of us.

10           At the last meeting that we had our  
11 pharmaceutical industry colleagues had the  
12 opportunity to conference over lunch and make a  
13 statement after lunch, and I wouldn't necessarily  
14 want to put undue pressure if they want a little  
15 more time to consider some comments.

16           DR. SANTANA: Anthony, yes?

17           DR. ELIAS: Yes, I just wanted to talk  
18 about a different matrix of sorts because we are  
19 talking about what do you do with rare diseases.  
20 One of the other matrices, of course, is that now  
21 many of the tumors in adult oncology are going to  
22 be subdivided. They are going to be subdivided in  
23 major ways based on gene array and we are really  
24 going to be starting to talk about pathways, what  
25 pathways are important. So, you are going to have

1 maybe EGFR being an important pathway across  
2 multiple disease histologies and maybe you will  
3 have a drug that is going to be approved for any  
4 tumor that is EGFR, that has that as an important  
5 pathway.

6           Now, we also do know that some of these  
7 pathways may be different within the context of the  
8 cellular milieu but, nonetheless, I think we may be  
9 completely reorganizing our oncology taxonomy and  
10 really be talking about pathways, which pathways  
11 are important. I think that may completely shift  
12 the types of indications people are going to be  
13 looking for and make what was once a very rare  
14 tumor into something extremely common.

15           DR. SANTANA: Yes, I want to follow up on  
16 that. I think, you know, historically the agency  
17 and the sponsors seek an indication for a very  
18 specific item -- you know, second-line salvage  
19 therapy for metastatic breast cancer; that is the  
20 indication; that is where they come forth. I think  
21 what you are suggesting, and I think we have  
22 thought a lot about that, is that maybe it is time  
23 for all of us to rethink that; that there may be  
24 some drugs or some biologics in which the  
25 indication which the sponsor seeks and that the

1 agency is after is very different. It is not the  
2 historical, traditional breast cancer salvage  
3 therapy for metastatic disease, but maybe some  
4 biologic event which this particular target agent  
5 targets.

6 DR. PAZDUR: We welcome that, and we could  
7 handle that by labeling. For example, a drug could  
8 be approved if it inhibits this enzyme in a variety  
9 of tumors. So, that can be handled by labeling.  
10 So, that is not an insurmountable problem for us to  
11 overcome and basically apply to a pediatric  
12 situation if there are tumors in the pediatric  
13 population that overexpress that --

14 DR. SANTANA: Yes, the challenge is to  
15 identify those.

16 DR. PAZDUR: But this has to be well  
17 defined by the scientific community, that this is a  
18 way to reclassify tumors. Remember, whenever we  
19 are mandating a company to do something it is a  
20 little bit different than just saying, "won't you  
21 do it? It would be nice." This carries a stick  
22 with it and repercussions for the company both  
23 financially and from a regulatory point of view.  
24 So, we have to have a sound scientific basis. It  
25 can't be on the basis of one report or a feeling

1 that these tumors may overexpress this issue. It  
2 has to be a recognition that there is a change in  
3 the taxonomy of how we deal with these tumors and  
4 the terminology.

5 DR. SANTANA: Yes, Donna?

6 DR. PRZEPIORKA: To follow up on a comment  
7 that you made regarding labeling, using as an  
8 indication inhibition of a particular enzyme or  
9 pathway, would that be outside the context of doing  
10 a full study to determine whether or not that  
11 pathways in, as Anthony put it, the cellular milieu  
12 is actually going to be effective? Would you still  
13 not require a specific disease indication?

14 DR. PAZDUR: No.

15 DR. HIRSCHFELD: We may not.

16 [Slide]

17 I put up a slide, which I had in reserve,  
18 which shows the type of principle and it echoes the  
19 same thinking that Dr. Elias articulated which we  
20 have been discussing for several months, and which  
21 we have discussed in previous meetings of this  
22 committee. It states in sort of broad terms that  
23 if a lesion -- and we haven't stated what a lesion  
24 may be but it could be a pathway, a translocation,  
25 overexpression of a particular gene, point mutation

1 -- is necessary for establishing or maintaining the  
2 malignant phenotype, and if a therapy is directed  
3 against that lesion, then studies in tumors where  
4 the lesion occurs and has the same critical role  
5 are warranted. So, there are a number of  
6 conditions. It shouldn't just appear in cells but  
7 it must play some central role in the pathogenesis  
8 of the tumor type. That is the type of general  
9 thinking that we would like to be moving toward and  
10 away from the more conventional, historical,  
11 traditional approach.

12 DR. PAZDUR: But this is going to require  
13 a great deal of work obviously and, you know, I  
14 don't expect a sponsor to come in and say, "okay,  
15 this is a target and we're just going to develop  
16 the drug only in this target" because they are  
17 subject to basically the same confines as we are --  
18 is this a well accepted change in the way  
19 physicians look at tumors?

20 How I would expect this to occur over  
21 time? Probably these targets will be identified in  
22 a particular tumor. When confidence develops that  
23 this is the way that the drug works, then this will  
24 be extended and we will kind of divest ourselves  
25 perhaps of the histological confirmation of tumors.

1 But I think it is going to be a multi-step process.  
2 It is not just going to be a bang -- this is the  
3 target and we will just develop drugs. I think it  
4 is going to be a step-wise evolution in how we look  
5 at things rather than a complete change in one  
6 study.

7 DR. HIRSCHFELD: And just one other point,  
8 our overriding and regulatory-derived principles  
9 must show patient benefit. So, the indication, I  
10 would expect, would never be for inhibition of EGFR  
11 in such-and-such a cell type. The indication would  
12 read for patient benefit for prolonging life in  
13 patients who have tumors that overexpress EGFR and  
14 have certain other characteristics, and all we  
15 would be doing is moving from a histologic  
16 description of the tumor to a more functional or  
17 biological description but it absolutely must show  
18 patient benefit.

19 DR. SANTANA: I think our colleagues from  
20 industry want to go ahead and make some comments.  
21 For the purpose of the record, please state your  
22 name and your affiliation.

23 DR. RACKOFF: I am Wayne Rackoff, a  
24 pediatric oncologist at Johnson & Johnson. I just  
25 wanted to make one comment and then Raj is going to

1 make a number of others, just to support what Steve  
2 said about the comment that Roger made about  
3 adverse events. This has come up, and I make this  
4 comment really as one of the co-chairs of the COG  
5 Industry Committee. It has come up in repeated  
6 conversations; it has come up in conversations with  
7 children's advocates and in our committee and here,  
8 and in the committee at COG it has come up and,  
9 Steve, we just want to support what you say, that  
10 there are no data that support that this has ever  
11 been an issue.

12 I think, just talking among ourselves  
13 especially with the number of pediatric oncologists  
14 who have entered clinical research and development  
15 within industry, it is not something that we hear a  
16 lot. There is always a concern, especially from  
17 our commercial counterparts, about how we will deal  
18 with toxicities in labeling and then in  
19 commercialization. But in research and development  
20 and in looking especially at the necessity of  
21 providing a clinical development plan for  
22 pediatrics when we come before the FDA, we know  
23 that there are pediatric oncologists within FDA who  
24 are sensitive to the issue that the labeling will  
25 have to reflect that a specific toxicity occurs

1 just in a subpopulation.

2           So, we hope that what Steve has said, and  
3 we will reiterate that over and over again at  
4 meetings as it comes up, that that is not and  
5 should not be a concern in inhibiting  
6 investigators, consumer advocates and families from  
7 coming to us and suggesting a study that would be  
8 appropriate in pediatrics.

9           DR. MALIK: I am Raj Malik, with Bristol  
10 Myers Squibb, also a pediatric oncologist. Just a  
11 couple of comments, and I am speaking on behalf of  
12 the COG Industry Advisory Council, and that has  
13 been a great forum for really establishing, I  
14 think, a new paradigm of collaboration between the  
15 COG, the NCI, CTAP, FDA, certainly patient  
16 advocates in terms of really addressing all the  
17 issues that are being discussed here.

18           I think one of the issues that was  
19 discussed at our last meeting was really the issue  
20 of prioritization, and I think it keeps on coming  
21 up over and over again because it speaks to, as Dr.  
22 Pazdur said, to the sound scientific rationale. It  
23 speaks to how are we going to take these 400 agents  
24 in development and pick up the best agents to  
25 develop in children. And, that is certainly a

1 process in which industry is also very interested  
2 in participating and I was very glad to hear from  
3 Dr. Smith that the first such meeting has already  
4 started and we, in industry, look forward to  
5 participating in that dialogue as well.

6           So, in general, you know, we are also very  
7 supportive of the efforts that are going on here  
8 and having a core of pediatric oncologists in  
9 industry right now I think makes for a very  
10 collaborative environment.

11           DR. SANTANA: Thank you for those very  
12 supportive comments. Yes?

13           DR. MELEMED: My name is Allen Melemed,  
14 with Eli Lilly. I just want to add one thing that  
15 wasn't stated. I hate to say this but we have  
16 somewhat of a bias because we are some of the  
17 larger pharmaceutical companies that are usually at  
18 these so there is somewhat of a resource issue from  
19 larger pharmaceuticals to smaller pharmaceuticals  
20 in the sense that we have more people, more  
21 pediatric oncologists in the company and they may  
22 not have the same resources to get the clinical  
23 trials, and they may not have the same resources as  
24 far as the actual drug supply. So, there is  
25 somewhat of a bias, obviously, with the larger

1 pharmaceuticals. So, it might be harder on the  
2 small biotechs where they have these new drugs that  
3 you want. So, that is one thing I wanted to say.

4           The other thing is the timing of the  
5 studies. The Pediatric Rule is a mandate. Now,  
6 the FDAMA is a bonus and an addition that you can  
7 get on exclusivity. That is a patent extension and  
8 that extension occurs at the end of the patent.  
9 So, you want and obviously we want pediatric  
10 oncology drugs now, but for FDAMA you can actually  
11 do studies at the end of the patent life or when  
12 the drug is already marketed. So, a lot of this  
13 doesn't address the incentive; it addresses the  
14 rule and that is why you have to be careful how you  
15 administer the rule.

16           DR. SANTANA: Anybody else have any  
17 comments? Malcolm?

18           DR. SMITH: I would have a question to  
19 Henry and others relating to the slide that Steve  
20 has put up. One of the slides mentioned a report  
21 of EGF receptor expression in the majority of  
22 pediatric gliomas but not the amplification of the  
23 gene. So, what data do we need then to say that  
24 this is a valid target for pediatric high grade  
25 gliomas or that it is just unrelated; it is there

1 but it is not really doing something, and how do we  
2 develop those data to inform us?

3 DR. FRIEDMAN: Specifically are you asking  
4 is the amplification going to be an issue or just  
5 the increased expression?

6 DR. SMITH: Well, that is my question.

7 DR. FRIEDMAN: Okay, what is the relevant  
8 parameter for a drug being effective, an EGFR  
9 inhibitor, for example, in this setting?

10 DR. SMITH: Right, how do we know? We  
11 know expression and what do we need to know to be  
12 more confident or to be confident that, in fact, an  
13 EGFR inhibitor would be a good drug to try in this  
14 population?

15 DR. FRIEDMAN: I think in any given  
16 situation the hope is going to be that there are  
17 trials being conducted to help answer that. In  
18 point of fact, for that particular question there  
19 are several trials, including one at Duke that  
20 specifically we will know in the space of 12-15  
21 months what is the relevance of EGFR amplification  
22 wild type versus mutant and increased expression  
23 without amplification versus activity of an EGFR  
24 inhibitor. And, there will be studies like that I  
25 think from a number of different sources. I am not

1 sure if that is going to be happening, Howard, with  
2 you or not at NCI, but I think that as we get a  
3 better idea of what biological parameter, in this  
4 case expression versus amplification, is critical  
5 we will be able to have the answer to your  
6 question. For that particular question probably 15  
7 months from now we will have the answer.

8 DR. SANTANA: Susan?

9 DR. COHN: Yes, I just wanted also to  
10 follow up. Malcolm, I think the meeting that you  
11 had yesterday, looking at these preclinical models,  
12 is certainly one thing that we will be very  
13 interested in looking at and seeing if that will  
14 correlate. So, I am sure it will be relatively  
15 simple to set up some preclinical models looking at  
16 EGFR expression versus amplification and then  
17 looking at efficacy of various targets to see if  
18 these models respond or don't respond. I would  
19 imagine that would be certainly a place to start in  
20 terms of prioritizing.

21 DR. LEVIN: If I may make a comment, I  
22 don't think it is so simple because the issue with  
23 some of these new molecules is to understand how to  
24 use them. I, for one, would say that it doesn't  
25 make much sense to give one of these inhibitors for

1 an amplified target like EGFR because you have the  
2 issue of conservation of mass. You have to knock  
3 down too many receptor tyrosine kinase sites than  
4 you can possibly do.

5 I think that a lot of the preclinical  
6 research done by industry and, hopefully, done by  
7 pediatric consortia and private academic  
8 institutions has to address the issue of, one, is  
9 the target really good; two, what is the optimum  
10 dose of these agents that needs to be given to  
11 inhibit the target, not what is the optimum dose to  
12 be given to produce the toxicity, the MTD that will  
13 then allow you to go forward. We need to  
14 understand exactly how these drugs work in order to  
15 use them well, and I think it is going to continue  
16 to be increasingly the goal of most successful  
17 pharmaceutical efforts and academic efforts to  
18 learn how to use these drugs so that they can be  
19 used in combination. I think that is going to  
20 require a commitment from industry, academia and  
21 the NIH. I do not think that the commitment need  
22 come from the FDA.

23 DR. FINE: To echo that and to follow up  
24 on the meeting that we had yesterday on the  
25 preclinical model, I would propose that that is

1 really the challenge to the pediatric academic  
2 community. If they want to have the Pediatric Rule  
3 more commonly come into play for access to better  
4 drugs, the onus is on us to actually show that  
5 these targets for these new drugs are validated  
6 targets for pediatric brain tumors and that the  
7 preclinical data supports their use, at which point  
8 then the Pediatric Rule simply comes into play. I  
9 am not sure it is necessarily the onus of the  
10 pharmaceutical industry to do that. So, if we want  
11 drugs for our children, I think it is within the  
12 academic community to make that preclinical data  
13 come to fruition.

14 DR. WEINER: From the parents' and  
15 patients' perspective, I think what we really want  
16 is reassurance that the science will prevail  
17 regardless of either the economic incentives or  
18 disincentives or regulatory environment. When we  
19 bring our kids into the clinic, it is the trust  
20 that the science will dictate those decisions  
21 rather than any other consideration and I think it  
22 is absolutely imperative that that is what prevails  
23 in this environment.

24 DR. SANTANA: Very appropriate comment.

25 DR. POMEROY: I think another aspect of

1 this that may be driven as we understand tumors  
2 better actually has applied to histologically based  
3 taxonomy of tumors as well, which is that there are  
4 some tumors, such as glioblastomas and high grade  
5 gliomas, that are very prevalent in adults where  
6 the development of treatments is very rapid and,  
7 yet, they are very rare in children. So, we end  
8 up, because of a numbers problem, not being able to  
9 conduct trials at the same pace.

10 I guess one question that will be raised,  
11 as we have these new inhibitor compounds and a new  
12 understanding at a molecular level of what is going  
13 on in these tumors, is are there ways that we could  
14 apply either statistically or by joint trials an  
15 efficacy trial which I think we all agree, at least  
16 I certainly agree, is the big issue for many  
17 pediatric brain tumors, more than toxicity. How  
18 can we include children in trials that move along  
19 quickly so when a new compound comes along we don't  
20 have to wait five years to test it? Because I  
21 think things are going to be moving along pretty  
22 quickly over the next ten years.

23 DR. SANTANA: Anthony?

24 DR. ELIAS: Yes, I would agree with  
25 Howard. I certainly don't think that the science

1 is yet there to be able to say that, for example,  
2 any time you see EGFR that is going to be an  
3 important pathway. I think our experience, for  
4 example, with anti-ras therapy with FCI is just a  
5 humbling case where it probably is the case that,  
6 in fact, the targets that we are targeting are  
7 actually not perhaps the targets that actually will  
8 work.

9           So, I think to a certain extent the  
10 principle of developing things where EGFR is, in  
11 fact, an important target or one other pathway is  
12 an important target across histologies is at least  
13 plausible. I think we are not there yet to be able  
14 to know what the gene patterns are, the milieu and  
15 so forth to be able to predict yet without actually  
16 testing it. In the future the hope will be that,  
17 in fact, certain gene patterns are going to be able  
18 to predict for response to certain types of  
19 interventions and that you will be able to tell but  
20 I don't think we are quite there yet.

21           DR. SANTANA: Robert?

22           DR. BENJAMIN: I would like to echo what  
23 Scott said from a sarcoma point of view. If we try  
24 to deal with specific pediatric studies in specific  
25 sarcomas, whether defined based on a molecular

1 abnormality or defined based on histology, there  
2 will never be enough children to study. Therefore,  
3 if a separate study needs to be done the children  
4 will never get the drug. I think the alternative  
5 strategy, which is really not addressed by the  
6 rules as I see them, is allowing for participation  
7 of human beings in studies of their cancers  
8 regardless of their age. I think that would allow  
9 children to get their drugs more quickly when it is  
10 appropriate.

11 DR. HIRSCHFELD: I think we recognize that  
12 and on a to be announced date we will specifically  
13 look at that issue of trial design and trial  
14 access.

15 DR. SANTANA: Roger?

16 DR. PACKER: I would certainly echo your  
17 comments as long as we set up those studies, and  
18 this goes back to trial design, to know what we are  
19 monitoring; that we can't always be monitoring the  
20 same things, such as lowering of blood count or  
21 elevation of liver functions. If you are going to  
22 be monitoring aspects of brain development and  
23 brain function differently in that population, I am  
24 certain on board with that.

25 I would still like to come back to that

1 principle that is up there, and the term that  
2 really keeps jumping out at me is "malignant  
3 phenotype." We are still missing a large grouping  
4 of patients and if we are going to be basing  
5 things, as we say, on a biologic basis and this  
6 receptor or this chemical being elevated in the  
7 specimen we are again going to be treating patients  
8 relatively late in the course of their illness.

9           One of the other things that I would like  
10 this committee to battle with and the FDA to help  
11 us to work with industry is how do we apply these  
12 things, again, at a time where they might be more  
13 effective -- going back to Dr. Levin's comments --  
14 not only in pediatrics but in adults at a time when  
15 the tumor has not mutated to GBM, where we may have  
16 not picked up the same markers and where we may not  
17 have strong biological rationalizations, except the  
18 clinical story will tell us that if we have a low  
19 toxicity molecule maybe we should apply it early in  
20 the course where we don't have compelling data yet  
21 that things are amplified? That is where I don't  
22 see these models helping us dramatically in getting  
23 that early application.

24           DR. LEVIN: I think you have to be a  
25 little careful though because we should be the same

1 as industry in some ways and we should be focusing  
2 on the target. So, say, for the lower grade tumors  
3 you find a set of target molecules, you should  
4 really be seeking your drug based on that. Some of  
5 the molecules that are out there, for instance EGF  
6 receptor inhibitors, might well work much, much  
7 better in that subpopulation. So, it is going to  
8 be up to somebody in academia to come forward with  
9 a hypothesis that says I can test this in animal  
10 systems or I can test it in cells, and it appears  
11 as if this is more likely to be effective in the  
12 subpopulation, therefore, I want access to the drug  
13 to test it against that population. The  
14 pharmaceutical company might say, well, there are  
15 only 50 patients a year with that disease; it  
16 doesn't financially pay, and what you are really  
17 asking then is, is there another mechanism by which  
18 you can get access to that chemical.

19 DR. PACKER: Let me just comment on that  
20 one other time. We have talked about a  
21 transformation of tumors from low grade to high  
22 grade and that has already been presented. There  
23 is a point in all of these tumors, we think,  
24 especially as they march along to glioblastoma  
25 multiforme, where they picked up some of their

1 transformation but maybe it is not high enough that  
2 we have been able to pick it up in a Petri dish.  
3 Those molecules may be extremely effective when  
4 there is a very low amplification, and if we are  
5 going to be stuck and have to wait until we can  
6 prove that we are going to miss the opportunity to  
7 impact on the disease early in the course, and we  
8 do a very bad job on impacting on disease later in  
9 the course and although these molecules may be  
10 wonderful, nothing yet has proved to me that when  
11 disease is rampant it is going to turn the disease  
12 off. And, I just want to know how to get at it not  
13 only early in a patient population but early in the  
14 course of the illness to the patient.

15 DR. HIRSCHFELD: I would like to ask Dr.  
16 Poplack if he could just address this because I  
17 know he has thought very much about this, and there  
18 are in the hematological malignancies conditions  
19 which are called preleukemic states and I would  
20 like you to make a comment as to whether therapy or  
21 intervening in these preleukemic states has thus  
22 far had any impact, or just how you would approach  
23 the problem.

24 DR. POPLACK: I think that there is  
25 certainly a need to apply therapy in some of the

1 preleukemic states. I am not sure whether we have  
2 analogies in brain tumors that would be appropriate  
3 for therapy, and I think probably appropriately we  
4 are focusing on the situations of greatest need.  
5 Whatever principle we adhere to or gets applied  
6 needs to be assessed and proven through these  
7 trials, and I think it would be more difficult,  
8 Roger, for us to be applying therapies to suspected  
9 or hypothetical situations where we don't have  
10 biological evidence even if there is a need. So, I  
11 am not sure how you would suggest that we would  
12 apply an agent, without having biological data,  
13 just because there is a need.

14 DR. SANTANA: Yes, and the challenge to  
15 identify those populations because you are now  
16 going to be targeting populations that don't have  
17 the complete spectrum of the disease. You are  
18 targeting at a very much earlier point and the  
19 challenge is to be very careful to identify those  
20 populations.

21 DR. PRZEPIORKA: In the hematologic group  
22 I think the one example that comes to my mind,  
23 because of recent action, is Gleevec where the  
24 tyrosine kinase inhibitor works wonderfully in the  
25 chronic phase of CML which we don't consider

1 potentially a full malignancy, but doesn't work  
2 anywhere near as well in blast crisis when there  
3 are so many other things that actually contribute  
4 to the malignant phenotype. The challenge, as  
5 Victor put it, is trying to identify what is going  
6 to be important early on, and studying the  
7 malignant cells will give us a whole array of  
8 possibilities but we have to figure out what is  
9 that one thing that early on we can step in there  
10 and really deal with.

11 I just wanted to make one additional  
12 comment. I think in planning the drug design  
13 meeting it is important to think about the public  
14 health interest in making sure the drugs are  
15 available also in adults with diseases that are  
16 prevalent in small numbers, the same way that we do  
17 with the pediatric groups.

18 DR. SANTANA: Dave?

19 DR. PARHAM: I think one thing we are  
20 going to have to come to grips with in this  
21 discussion is that in the groups of neoplasms we  
22 are discussing there is no analogy to preleukemia.  
23 All of these tumors develop in a full-blown  
24 malignant fashion, particularly in sarcomas. Even  
25 in the brain tumors fibrillary astrocytomas are

1 very, very uncommon and by the time they announce  
2 themselves as tumors they are full-blown  
3 malignancies or else they are pilocytic  
4 astrocytomas which very rarely later on develop a  
5 malignant phenotype. So, I am not sure that  
6 discussion is going to be helpful here because  
7 there are no identified pre-malignant stages in  
8 these tumors.

9 DR. SANTANA: Good. I am going to go  
10 ahead and ask that we take a break. We have had a  
11 very good discussion. Let me summarize two points  
12 in very general terms that I perceived from the  
13 discussion this morning with a lot of detail. One,  
14 I think through this whole discussion through all  
15 these meetings, it is important, like somebody has  
16 reminded us, that the endpoints don't change  
17 whether we are talking about the Pediatric Rule or  
18 any other mandate. We are still looking at  
19 bringing forth treatments that are scientifically  
20 based with a good rationale and that ultimately  
21 demonstrate some efficacy and some benefit for the  
22 patients. So, I think that is a central point in  
23 this discussion.

24 The second thing that I think is very  
25 important to recognize is that it is encouraging to

1 hear that both the agency and other federal  
2 agencies that deal with pediatric oncology and  
3 sponsors are willing to start thinking outside of  
4 the famous box in developing probably other models  
5 with some of these new biologics and some new  
6 principles that potentially could apply. So, it is  
7 very encouraging to hear that we are moving into a  
8 different phase and that the agency is willing to  
9 consider these proposals in a very different way.

10 I think we have talked about the general  
11 things this morning. After the break we will  
12 specifically start addressing some tumor types.  
13 So, let's go ahead and take a 15-minute break and  
14 reconvene at 10:15. Thank you.

15 [Brief recess]

16 DR. SANTANA: We are going to go from the  
17 general now to the specifics. The first session in  
18 which we are going to try to address issues is on  
19 sarcomas. Before we get started, I am going to ask  
20 Karen to just briefly give us some instructions  
21 about lunch. Then after that, any members who  
22 joined us after we started this morning do need to  
23 introduce themselves for the public record. So, I  
24 will ask those of you who came a little bit late  
25 who did not introduce yourselves this morning to do

1 that. Karen?

2 DR. TEMPLETON-SOMERS: We have made  
3 arrangements for those of you at the table to be  
4 allowed into the Parklawn Building. So, you can  
5 pretend you are a regular federal employee and eat  
6 in our cafeteria, which is the most convenient  
7 place. You are not obligated to go there but it is  
8 quick --

9 DR. SANTANA: It is an honor!

10 [Laughter]

11 DR. TEMPLETON-SOMERS: It is an honor,  
12 yes! Victor has been there before and he is  
13 willing to go back.

14 DR. SANTANA: Stick with the salads!

15 [Laughter]

16 So, when we are done with the morning  
17 session we will just walk over there and Karen has  
18 arranged for some stickers because we have to go  
19 through security over there too.

20 Any committee members that joined us late,  
21 could you please introduce yourself for the public  
22 record by stating your name and affiliation?

23 DR. KAYE: Frederic Kaye, from Centers of  
24 Cancer Research, NCI and the Naval Hospital.

25 DR. SANTANA: Thank you.

1 MS. KEENE: Nancy Keene.

2 DR. SANTANA: Patient. Thank you, Nancy.  
3 We are going to get started. Our first  
4 presentation is by Mike Link, from Stanford. Mike?

5 Perspectives on Sarcoma

6 DR. LINK: Well, first I would like to  
7 thank the committee. I am flattered to be asked to  
8 speak here and, as I understood my charge, which I  
9 may not have understood, I was going to give some  
10 perspective on sarcomas to set the tone for some  
11 discussion.

12 [Slide]

13 As such, I will give a brief tour of the  
14 sarcomas to provide some background at least from  
15 the pediatric perspective. I talked with Bob  
16 before and I hope that he will fill out those  
17 aspects that we don't like to deal with.

18 [Slide]

19 So, I am going to give you some themes.  
20 This is not the conclusion slide, this is the  
21 themes, sort of the punch line that I might as well  
22 get to right at the start. First of all, sarcomas  
23 are a heterogeneous collection of diseases and  
24 families of diseases so that we shouldn't be  
25 thinking of them as a group.

1           The individual diseases and families may  
2 be defined molecularly and a molecular derangement  
3 characterizes each tumor type usually so that in  
4 the ones where it has been explored there is often  
5 a particular molecular derangement which defines  
6 the malignancy, and this derangement in most of our  
7 minds, even if not in minds of all pathologists,  
8 supersedes system morphology in defining the  
9 disease. So, we are now defining the disease on a  
10 molecular basis.

11           It is unlikely, however, that the  
12 characteristic molecular derangement is the entire  
13 story. So, obviously, one molecular derangement  
14 doesn't make a summer, to paraphrase that, and I  
15 think obviously we are learning from further gene  
16 array studies that there is a lot more that goes on  
17 beyond the initial event.

18           But one thing that is important for this  
19 particular discussion is that I think that these  
20 are prototypic diseases which span the child and  
21 young adult age range. So, this is a disease of  
22 children and young adults and so obvious for this  
23 particular kind of discussion.

24           [Slide]

25           From that, I am just going to proceed to

1 the usual background talk. This is a small piece  
2 of the action in children as it is in adults. So,  
3 it is only those red things, about 11 percent of  
4 all the tumors we are talking about are the soft  
5 tissue and bone sarcomas.

6 [Slide]

7 The way that I think most pediatricians  
8 think of them, although I will be glad to be  
9 corrected by others in the room, is that we divide  
10 them into essentially three groups of tumors, three  
11 major groups, the osteosarcoma; the Ewing's family  
12 of tumors which is bone and soft tissue tumor and  
13 includes peripheral primitive neuroepidermal tumors  
14 and others, and I will go into that to show you  
15 that this is a family of tumors that has now been  
16 unified by a molecular concept; and then a group of  
17 tumors that has been disunited perhaps by every  
18 factor that we can think of, the soft tissue  
19 sarcomas, the non-rhabdomyosarcoma soft tissue  
20 sarcomas, about which I will have very little to  
21 say, relying on Bob for that; and rhabdomyosarcoma  
22 which we know is heterogeneous in itself because it  
23 includes embryonal rhabdomyosarcoma and alveolar  
24 rhabdomyosarcoma which, I will show you, are very  
25 different diseases even though we treat them with

1 the same treatment strategies, and other variants  
2 which are probably less important because they are  
3 very rare.

4 [Slide]

5 I do want to leave you the impression that  
6 we have made progress in these diseases and, in  
7 fact, some of the progress that we have made is one  
8 of the problems in terms of new drug development.  
9 This is the history of, let's say, the overall  
10 five-year survival in the three major groups of  
11 sarcomas, rhabdomyosarcoma, osteosarcoma and  
12 Ewing's sarcoma which appear in childhood. This  
13 was in an article in The New England Journal of  
14 Medicine showing progress over time. As you can  
15 see, with the current state of the art there are,  
16 fortunately, fewer patients left who are candidates  
17 for experimental therapies at least as front-line  
18 treatment.

19 [Slide]

20 I am going to start with osteosarcoma and  
21 not say too much about it because Bob Benjamin is  
22 also an expert here, but I just wanted to  
23 demonstrate that age of onset of the disease  
24 probably tells the story, more than anything  
25 better, why this is a disease that adults and

1 pediatric patients should be considered together.  
2 As has been stated before, I don't know that there  
3 is much difference between a child in the second  
4 decade or an adult in the third decade of life in  
5 the behavior of the disease, assuming that we are  
6 talking about classic osteosarcoma.

7 [Slide]

8 There are some molecular derangements in  
9 osteosarcoma, although I think that most of us  
10 would agree that not a single one of them unifies  
11 the disease in the way that I will show you for the  
12 other sarcomas, but there are mutations in RB gene  
13 and p53 mutations which are certainly  
14 characteristic of a minority of patients; MDM2  
15 amplification and, through this, inactivation of  
16 p53 which occurs in a minority of patients and  
17 overexpression of Her2 which is an important  
18 therapeutic target, but not in all patients. I  
19 think, again, no single molecular derangement  
20 defines this group of diseases.

21 [Slide]

22 I understood that I was supposed to give  
23 you the state of the art or the state of the  
24 therapies that we have and I am going to give you  
25 two slides which show the unfortunate circumstance,

1 as we talked about earlier, where we are able to do  
2 perhaps in the best of circumstances a trial every  
3 four to five years. We haven't necessarily always  
4 been able to accomplish that but even when we have,  
5 this is the outcome of a trial that I ran between  
6 1981 and 1986 with a long-term event-free survival  
7 of somewhere in the neighborhood of 57 percent but  
8 a 4-year event-free survival, as you can see, of  
9 somewhere near 60-some percent.

10 [Slide]

11 Then a trial that Paul Meyers, who I am  
12 sitting next to, just finished running, from 1993  
13 to 1997 and the overall outcome is pretty much  
14 superimposable on the curves that I just showed  
15 you. So, a couple of decades of work and not much  
16 progress in terms of the number of patients that  
17 are cured.

18 [Slide]

19 A group of patients who we also have not  
20 made much progress against is patients with  
21 metastatic disease. Staging of bone tumors is  
22 pretty easy. They either have metastases or they  
23 don't that are clinically evident. This is a group  
24 of patients where about 20 percent of them are  
25 cured. They fare poorly even with modern

1 treatments and are, obviously, appropriate  
2 candidates for new approaches as first-line  
3 therapy.

4 [Slide]

5 Now I am going to turn to the second  
6 category, Ewing's sarcoma, similarly a disease of  
7 young adults and children but where the curve is  
8 shifted dramatically more to the left. So, I think  
9 that most of the adult oncologists would agree that  
10 we probably know more about it or at least have  
11 more experience with it than our adult oncology  
12 colleagues.

13 [Slide]

14 Here we have the first of a group of  
15 diseases where there is a molecular derangement  
16 which characterizes the disease and underpins  
17 tumorigenesis. Ewing's family of tumors is  
18 characterized on the right, as you can see, with a  
19 chromosomal translocation between chromosomes 11  
20 and 22 usually, which produces a fusion gene and  
21 gene product which characterizes about 95 percent  
22 of cases of Ewing's sarcoma in the tumor cells, and  
23 is felt to be a felt and malignant transformation.  
24 On the left you see an analogous transformation  
25 which I will return to in discussing alveolar

1 rhabdomyosarcoma.

2 [Slide]

3 So, this is a reciprocal translocation  
4 found consistently in all of the family of Ewing's  
5 sarcomas. So, soft tissue Ewing's, PNETs tumors,  
6 all of the diseases that have had various different  
7 names but now are unified together. Through EWS is  
8 fused FLY1 or ERG, the two common partner genes,  
9 and this translocation results in a  
10 tumor-associated fusion gene which can be detected  
11 by a variety of techniques in virtually all cases  
12 and, therefore, has become sort of a diagnostic  
13 test which we use to diagnose the malignancy often  
14 more rapidly than we can get an answer from our  
15 pathologists.

16 [Slide]

17 What is the state of the art? Again,  
18 about two-thirds of the patients with no evidence  
19 of metastatic disease are cured compared to  
20 patients presenting with metastases that are overt  
21 where somewhere in the neighborhood of 20-15  
22 percent of the patients are cured. Again, the same  
23 theme as I said for osteosarcoma, a group of  
24 patients where we need better approaches.

25 [Slide]

1                   But there are some confounding variables.  
2 This is a site-specific tumor. Patients with  
3 certain sites do better than others. I am not  
4 going to show all of them here but there are  
5 obviously confounding variables in this related to  
6 tumor size and presence of metastases, etc. which  
7 contribute to this, but they have to be considered  
8 separately and is one of the caveats when we talk  
9 about just lumping patients together.

10                   [Slide]

11                   Here is another theme that will recur,  
12 although we think they are the same diseases, I  
13 believe, in older patients and younger patients,  
14 but there is a theme where, again, younger patients  
15 do better. Children less than nine years of age  
16 fare significantly better than older adolescents  
17 and young adults. I will get back to this -- I  
18 don't know if it qualifies as one of the pitfalls  
19 but is certainly one of the caveats that we have to  
20 think about in terms of lumping tumors in older  
21 patients and younger patients together even if they  
22 have the same molecular underpinning.

23                   [Slide]

24                   Now, the soft tissue sarcomas --  
25 rhabdomyosarcoma is the most common soft tissue

1 sarcoma in children.

2 [Slide]

3 More so than even Ewing's sarcoma, this is  
4 a disease of young children, although I don't know  
5 if it shows up on this slide. Part of the problem  
6 with this slide, of course, is that many of the  
7 studies of rhabdomyosarcoma entered patients for a  
8 while only up until age 21. So, I am not sure that  
9 we really know what the incidence is. There are  
10 clearly a lot of young adults out there with  
11 rhabdomyosarcoma but they have not appeared on  
12 clinical trials so they are essentially lost to us  
13 in terms of understanding them very well. But here  
14 you can see that the majority of kids are  
15 presenting younger than age nine, and certainly the  
16 overwhelming majority younger than age 15.

17 [Slide]

18 Here it is very clear that this is at  
19 least two diseases, even just by histomorphology  
20 and we know that there is an alveolar and embryonal  
21 subtype. Although until now most of the principles  
22 of therapy have been shared between the two, it is  
23 pretty clear that these two diseases are quite  
24 different, and it is not necessarily clear why we  
25 lump them except that because of the problems of

1 limited numbers of patients we often do so for  
2 convenience and to get more robust clinical numbers  
3 for our trials.

4           But it is important, as you can see if you  
5 look at the BOTR, which is a botryoid which is  
6 another version of embryonal, and lump that yellow  
7 curve with the green curve which is embryonal and  
8 then compare that to the lowest curve, the gold  
9 curve, which is the alveolar histology, you can see  
10 that this is really a very significant difference  
11 in outcome depending on histology. So, it is an  
12 important difference clinically.

13           [Slide]

14           Of course, as I have shown you, the  
15 alveolar variant is associated with a chromosomal  
16 translocation and the production of a fusion gene  
17 unique to alveolar rhabdomyosarcoma.

18           [Slide]

19           If you look at the lower half of this  
20 slide, this translocation, 2:13, is similar or  
21 analogous to Ewing's sarcoma fusion gene, PAX3 to  
22 one of the fork-head transcription factor members,  
23 and there is an infrequent similar translocation  
24 that involves PAX7 and FKHR, which I will talk  
25 about in a minute. So, there are two very, very

1 similar translocations which characterize alveolar  
2 rhabdomyosarcoma, and there are some cases that  
3 don't have or at least have no detectable  
4 translocation at all -- very different from  
5 embryonal rhabdomyosarcoma where certainly no  
6 clear-cut gene has been identified that  
7 characterizes the disease.

8 [Slide]

9 Now, even the difference in the  
10 translocation has an impact on the outcome of the  
11 patients. So, the more common PAX3 involved, the  
12 orange curve -- if we just look at patients with  
13 metastatic disease, those patients fare terribly,  
14 whereas those that have the alternative  
15 translocation involving PAX7 actually do quite  
16 well. So, again, we have to be very careful in  
17 terms of defining the disease based on a fusion  
18 gene because we think has variations in the fusion  
19 gene do make a difference. I think, although it is  
20 not entirely clear that everybody believes it but  
21 in the Ewing's sarcoma there are variants of the  
22 translocation and it seems that different break  
23 points in translocation are associated with more  
24 favorable or less favorable outcomes.

25 [Slide]

1                   Once again, we have made progress overall  
2   in rhabdomyosarcoma but when we look at how we are  
3   doing lately it is pretty much the same, about  
4   65-70 percent of children presenting with  
5   non-metastatic rhabdomyosarcoma are cured, although  
6   in the results of our last study, which was  
7   published just recently in The Journal of Clinical  
8   Oncology, there is no difference in outcome. When  
9   we use three different regimens all of the drugs  
10  have activity but there is no improvement in  
11  outcome by regimen.

12                   [Slide]

13                   Now, rhabdomyosarcoma is a disease that is  
14  unique in one way, and that is the disease behaves  
15  very differently depending on the site of  
16  involvement, and this makes one of the difficulties  
17  in talking to adult counterparts where they have  
18  site-specific diseases like breast cancer or bowel  
19  cancer. This is a different disease at any of the  
20  sites and it occurs in a multitude of sites.

21                   [Slide]

22                   If you look at the outcome by site, and I  
23  am not going to belabor each of these things but  
24  you can see that the outcome varies from 90  
25  percent, the top curve, to more like 60 percent for

1 other presentations and this putatively is the same  
2 disease. So, again, we have the problem that  
3 although we think we know how to define this  
4 disease, it is very different in its behavior  
5 depending on a number of different factors.

6 [Slide]

7 Then, a recurrence of this theme in terms  
8 of the impact of age, we know that older patients  
9 do less well, as I will show you, and part of the  
10 reason for that is because if you look at the  
11 incidence of alveolar rhabdomyosarcoma, which I  
12 have shown you is an adverse prognostic factor, the  
13 incidence of alveolar is higher in older children,  
14 33 percent for example in children older than 10  
15 years of age compared to only 18 percent in  
16 children in the 1-9 age group. So, a highly  
17 significant difference.

18 [Slide]

19 Even stage of presentation -- older kids  
20 much more frequently present with advanced stage  
21 disease, again accounting for why older children  
22 may do less well.

23 [Slide]

24 If we summarize what happens in older kids  
25 with rhabdomyosarcoma, they have a lot of things

1 that make them less favorable which may or may not  
2 have to do with the underlying biology of the  
3 tumors that occur in older children. So, they more  
4 frequently have alveolar tumors; tumors arising in  
5 extremity, which is a bad site; larger tumors; more  
6 invasive tumors; more regional spread and more  
7 metastatic spread. So, not surprisingly, they do  
8 less well. So, the question is, is this a feature  
9 of a different disease in older children or are  
10 there really fundamental biological differences,  
11 analogous to some of the things we saw in brain  
12 tumors that Henry showed?

13 [Slide]

14 This is just to demonstrate the relapse  
15 hazard. So, the lower this curve, the better the  
16 patients do. As you can see, it goes up both in  
17 very young children and older children, showing  
18 that those patients are much more at risk to  
19 relapse.

20 [Slide]

21 Now I am just going to make a brief foray  
22 into an area where I know very little, and most  
23 pediatricians don't know very much and I hope Bob  
24 will talk more about these, but when we talk about  
25 the soft tissue sarcomas of children and you take

1 out rhabdomyosarcoma and its variants and soft  
2 tissue versions of the Ewing's family of tumor, we  
3 are left with just a long list. I think Bob's is  
4 longer than mine, but these are the ones that occur  
5 in children and they are very, very heterogeneous  
6 in their histologic appearance, their behavior,  
7 etc., but the common ones that we see are synovial  
8 sarcoma. The ones I want you to focus on are -- it  
9 is not even up there, but a couple of the others  
10 that are important and I will show you the reason  
11 in the next couple of slides.

12 [Slide]

13 The reason is that similar to Ewing's PNET  
14 and alveolar rhabdomyosarcoma, some of these soft  
15 tissue sarcomas are now also molecularly definable.  
16 So, we can group them. For example, desmoplastic  
17 small round cell tumor, characteristic  
18 translocation, characteristic genes involved and,  
19 actually, they are kind of familiar because the EWS  
20 gene is involved in this tumor as well although  
21 fused to another partner, Wilm's tumor gene, so  
22 another pediatric partner is chosen. Similarly,  
23 synovial sarcoma and congenital fibrosarcoma also  
24 have very characteristic translocations -- again,  
25 titillating in terms of the fact that we can define

1 the diseases and also have a potential target for  
2 intervention.

3 [Slide]

4 My last slide on soft tissue sarcoma, just  
5 to show that, number one, children without  
6 metastases do very well; number two, that  
7 interventions beyond surgery and radiation therapy  
8 haven't made much of an impact that we know about.  
9 I suspect there has been some impact overall in  
10 adults but for a pediatrician it would be difficult  
11 to be convincing, although it may be convincing to  
12 an adult oncologist. The differences are quite  
13 small.

14 [Slide]

15 So, having said all that, what are the  
16 considerations when we try to link pediatric and  
17 adult patients with sarcomas? We can say that the  
18 diseases occur in children, adolescents and young  
19 adults, excluding, let's say, the  
20 non-rhabdomyosarcoma, the soft tissue sarcomas  
21 which occur in older adults as well, but these are  
22 basically diseases in a group of patients which  
23 span the adult and pediatric ages.

24 I think we could say that the diseases in  
25 adults and children may be similar on a molecular

1 level. I don't think there is any evidence that  
2 adults, at least for the fundamental  
3 translocations, have a different translocation but  
4 there is obvious heterogeneity even within each of  
5 these major subclasses of sarcomas, even  
6 histologically, biologically. There are different  
7 outcomes. And, it is pretty clear that there are  
8 other significant molecular derangements and  
9 differences in gene expression which will be likely  
10 to be determined, if they haven't already been  
11 determined, which distinguish patients even within  
12 a category and probably older patients from younger  
13 patients.

14 [Slide]

15 What are some of the other considerations?

16 Well, as you have heard in the talks in this  
17 session, there are limited numbers of patients  
18 available to begin with. There are hundreds of  
19 patients with these tumors, not thousands of  
20 patients each year in the United States newly  
21 diagnosed. We cure a relatively high proportion of  
22 them with current therapy so that there is  
23 limitation on what subjects are available for  
24 experimental therapies. Not to say that we  
25 wouldn't be interested in incorporating an

1 experimental therapy, but it does make it difficult  
2 to try to decide how you are going to cut back on  
3 what we know is curative for two-thirds of the  
4 patients. Therefore, it seems obvious that we  
5 should be combining efforts among adult and  
6 pediatric patients where the disease really appears  
7 to be a continuum encompassing pediatric and adult  
8 patients.

9 [Slide]

10 So, what are some of the other problems?  
11 Older patients fare less well in all varieties of  
12 sarcoma virtually. How do you explain that? Well,  
13 are there really true age-related biological  
14 differences? In other words, are older age  
15 patients associated with other features of the  
16 tumor itself that may not be defined by the primary  
17 translocation but other molecules that have yet to  
18 be defined that may be different in older patients  
19 and younger? It wouldn't be surprising.

20 Age remains independently prognostic in  
21 the studies that I have shown you. This may be  
22 also a reflection of host tolerance to therapy.  
23 So, it is a difference in host rather than  
24 difference in tumor. It may be a difference in  
25 compliance with intensive therapy. We know that

1 improvements in outcome have resulted from  
2 therapies which are pretty hard to give and if you  
3 had a choice, which a child may not often have,  
4 they may not always come in on time. And, there  
5 may be differences in physician compliance with  
6 intensive therapy.

7           So, it is not even a patient or a tumor  
8 issue; it is a doctor issue, and the mind set of a  
9 medical versus a pediatric oncologist, perhaps best  
10 demonstrated in a trial of treating adolescents  
11 with leukemia and the difference in results in a  
12 pediatric trial or a cooperative group trial that  
13 was presented at ASH in December are very  
14 compelling results, which showed very, very  
15 different outcomes, probably a difference resulting  
16 from doctor rather than fundamental biologic  
17 differences in the tumors.

18           [Slide]

19           I just wanted to conclude. So, these  
20 molecules that we have seen, and some of them kind  
21 of not primary targets for the therapies that have  
22 been developed, certainly present themselves as  
23 things that we ought to be interested in. For  
24 example, osteosarcoma -- Her2 is expressed and in  
25 those tumors Herceptin would seem to be a logical

1 potential intervention, not something that was  
2 developed with osteosarcoma in mind. The PDGF  
3 signal transduction pathway is blockaded by  
4 STI-571, again not a primary reason for the  
5 development of the drug but a reason to test it in  
6 osteosarcoma. Of course, for those tumors that  
7 have p53 and RB abnormalities, those might be  
8 suitable targets.

9           In rhabdomyosarcoma the fusion genes would  
10 be an interesting target either from immunologic  
11 approaches or from small molecule approaches. A  
12 similar case could be made for the Ewing's family  
13 of tumors and its specific characteristic  
14 translocation, and also in Ewing's the stem cell  
15 factor c-Kit signal transduction pathway could be  
16 blockaded by STI, again another application of a  
17 drug not developed specifically for that.

18           Desmoplastic small round cell tumor is not  
19 exactly a public health menace but it is a pretty  
20 nasty thing if you have it. Again, PDGF is  
21 putatively expressed in these tumors and might be a  
22 target for STI. I showed you some of the fusion  
23 genes involved in some of the other soft tissue  
24 sarcomas which we obviously be potential targets  
25 for new therapies.

1                   Hopefully, I have given some of the  
2 reasons why we should be thinking in terms of  
3 unifying these but understanding, of course, that  
4 there are differences in adults and children and  
5 their outcomes which may present not necessarily  
6 obstacles but just food for thought before we can  
7 willy-nilly make the recommendation that these  
8 should be combined.

9                   DR. SANTANA: Thanks, Mike. We will hold  
10 questions until we have the second presentation. I  
11 am going to invite Dr. Benjamin, from M.D.  
12 Anderson.

13   Perspectives and Background

14                   DR. BENJAMIN: I use a Mac, which is  
15 intuitively obvious rather than this machine which  
16 is not.

17   [Slide]

18   This is just a picture of M.D. Anderson.

19   [Slide]

20                   I am going to talk to you a little bit  
21 about the adult soft tissue sarcomas. Mike and I  
22 did talk in the beginning and I thought that,  
23 rather than overlapping, I would give you a very  
24 different perspective, and my perspective is that  
25 everything that you are talking about for

1   pediatrics applies in spades to sarcomas in adults.  
2   So, the question is how do you define these tumors?  
3   Should they be defined by patient age, histologic  
4   type, molecular abnormalities or whatever?

5                   [Slide]

6                   Sarcomas are extraordinarily rare tumors,  
7   less than one percent of all malignancies.  Mike's  
8   slide showed you that it is about 10 percent of  
9   pediatric malignancies, so a higher proportion but  
10  smaller numbers.  And, it is the smaller numbers  
11  that really kills us in terms of progressing in  
12  terms of knowledge in the treatment of these  
13  diseases.

14                  I made the comment once that you wouldn't  
15  treat adenocarcinomas all the same way, would you?  
16  And, that came back to haunt me at a meeting that I  
17  was at in Europe, but no medical oncologist would  
18  think of treating adenocarcinoma of the breast the  
19  same way as adenocarcinoma of the colon.  They are  
20  totally different diseases.  Yet, if you asked  
21  people about treating soft tissue sarcomas, they  
22  are one disease.

23                  [Slide]

24                  Well, here is the one disease; there are  
25  probably 50.  In fact, there has never been a study

1 which has adequately addressed the diversity within  
2 soft tissue sarcomas in adults, let alone put in  
3 the pediatric counterpart. Now, what was just  
4 presented to you very elegantly by Mike Link is  
5 that the pediatricians have done studies in  
6 osteosarcoma, single disease -- group of diseases  
7 but single group. They have done studies in the  
8 Ewing's family of tumors, relatively homogeneous  
9 group. They have done studies in  
10 rhabdomyosarcomas, some heterogeneity but  
11 relatively homogeneous group. The rest of the  
12 studies, the studies in adults are all done in  
13 "soft tissue sarcomas" and there are 25 different  
14 varieties or 50, depending on how you define them  
15 on a histologic level, not even at a molecular  
16 level.

17 [Slide]

18 You have already seen an updated version  
19 on this. Many tumors do have specific  
20 translocations. The ones in the pediatric age  
21 group tend to have more, but I can point out for  
22 you myxoid liposarcoma, which is a disease which is  
23 almost exclusively an adult disease but which has a  
24 specific translocation; synovial sarcomas which  
25 occur certainly more frequently in adults;

1 that was proposed, the clinical differences between  
2 these two tumors are so different. So, for us to  
3 go back and, don't forget, mandate a company to say  
4 that this is the same indication would be very  
5 difficult to do and we could be challenged on this.

6 DR. SANTANA: I think, Mike, the  
7 principles are basically the same. It is just that  
8 the diseases are different and they have to be  
9 taken on a case by case basis. I think that is  
10 what we are saying. In this particular case the  
11 differences are so obvious that I would feel  
12 comfortable saying the disease is technically the  
13 same and, therefore, whenever anybody from industry  
14 comes to the FDA saying I have a new drug or a new  
15 product for small cell lung cancer that the agency  
16 would mandate that they do studies in  
17 neuroblastoma. To me that would be a step --

18 DR. LINK: Too big a step.

19 DR. SANTANA: Too big a step.

20 DR. HIRSCHFELD: Unfortunately, our  
21 knowledge is not the state of physics where I  
22 think, much as we might like to have a unifying  
23 principles, we couldn't come to that. So, that is  
24 why we left open the possibility for nuances or  
25 corollaries of some general schema, which is why we

1 asked the same question multiple times.

2           Now, to refine this a bit further, and it  
3 might help looking at part B of this, should we  
4 then think of, for instance, the refractory setting  
5 and might that be different than the first-line  
6 setting?

7           DR. SANTANA: I will get to that. I think  
8 Anthony had a comment or a question.

9           DR. ELIAS: Not a major one. I think it  
10 is just where the burden of proof lies. I think  
11 the principles are the same and I agree with your  
12 statement, Victor, but basically these two diseases  
13 are so different that all you can really rest on is  
14 if you have commonalities in particular pathways.  
15 In the sarcoma situation you obviously have a lot  
16 more similarities and the burden of proof is not  
17 that you have to prove that these share the  
18 commonality pathway; you can make that assumption  
19 reasonably.

20           DR. SANTANA: Steve, I want to explore  
21 your comment a little bit further. You are  
22 suggesting that in the relapse setting the  
23 principle should be different? Run that by me one  
24 more time.

25           DR. HIRSCHFELD: I was just raising the

1 question that perhaps in the relapse setting we  
2 might have a different perspective on it than in a  
3 more global addressing of the two disease entities  
4 or of these neuroendocrine tumors.

5 DR. SANTANA: Malcolm, think about that  
6 one.

7 DR. SMITH: Yes, I thought that the  
8 purpose of the exercise was not to describe how an  
9 agent should be studied in children or population  
10 that should be studied. So, I wouldn't see the  
11 purpose of this committee to say you should study  
12 it in a relapse setting but not in a newly  
13 diagnosed setting but say it does or doesn't  
14 warrant evaluation for neuroblastoma.

15 DR. HIRSCHFELD: Right, but that is if you  
16 believe that all neuroblastomas are of the same  
17 flavor. But if you postulate that the diseases  
18 that lead to relapse are different than the ones  
19 which don't, then you could I think logically  
20 extend to saying, well, that would be something  
21 else again and we happen to call it neuroblastoma  
22 but maybe we should call it neuroblastoma variant,  
23 or some other thing. I don't want to get into a  
24 semantic argument; I just want to raise the  
25 question. And, if the answer is, no, we should

1 continue to consolidate, then that is the  
2 recommendation.

3 DR. SANTANA: I feel very uncomfortable  
4 with that, Steve, and I can't give you a strong  
5 argument. I am going to have to think through it,  
6 but my gut feeling is that I feel very  
7 uncomfortable with that train of thought. I think  
8 Donna had a comment and I will get back to you in a  
9 minute, Mike.

10 DR. PRZEPIORKA: Trying to get back to the  
11 request to keep the unifying principles the same  
12 throughout, I think that can be done because I  
13 think what we had talked about in answering  
14 questions A and B with the sarcomas in the design  
15 of the clinical trial was would you put pediatric  
16 and adult patients with such-and-such sarcoma in  
17 one study, and our experts said, gee, we would  
18 treat them the same way and they act the same way,  
19 why not? So, in lumping sarcomas as a term, it  
20 appeared that from a clinical perspective they were  
21 truly the same disease.

22 I think in this instance we are talking  
23 about a much larger pot. So, I would not conceive  
24 of somebody coming to the agency and saying, well,  
25 we have a drug for a neuroendocrine tumors and then

1 lumping pediatric and adult neuroendocrine tumors  
2 together. I think this is a situation where the  
3 neuroendocrine tumors in the pediatric population  
4 clinically are different rather than just  
5 pathologically and histologically and molecularly.  
6 So, there may be some rationale to keep those  
7 diseases on different protocols, but if there is a  
8 molecular target in the adult situation which is  
9 the same as in the pediatric population, that is  
10 where the rule should be mandated to do additional  
11 studies, not put them in the same protocol.

12 DR. SANTANA: Mike, do you have a comment?

13 DR. LINK: I guess I am confused now. If  
14 you had a cytotoxic drug that had an 80 percent  
15 response rate in non-small cell lung cancer would  
16 you mandate that they do pediatric trials because  
17 this is such a great drug? You wouldn't care?

18 DR. PAZDUR: That is not the question.

19 DR. LINK: I understand the question but I  
20 am just saying in general principles, if a drug is  
21 active --

22 DR. PAZDUR: Of course, we would care. We  
23 have to follow the law. Okay? And, the law is not  
24 what we want it to be; it is what is written on the  
25 books here and it clearly states that the

1 indication has to be the same. So, although we  
2 would encourage sponsors to do it -- here, again, I  
3 think this is a principle that I would like to get  
4 across, remember, we are mandating companies to do  
5 this so they can question us in a court of law  
6 regarding our interpretation of this and, believe  
7 me, if we stretch this it would lead to litigation  
8 regarding this. I guarantee you.

9 DR. SANTANA: You would have to serve as  
10 expert witnesses.

11 DR. PAZDUR: So, what we want and what we  
12 think is academically interesting, for example,  
13 yes, if a drug had activity in small cell lung  
14 cancer I would like to see it studied in  
15 neuroblastoma. I think it would be potentially an  
16 interesting drug and perhaps an active drug, but  
17 can we mandate that they do this? That is a  
18 different situation and we have to live within the  
19 confines of the law rather than what we think would  
20 be academically interesting.

21 DR. HIRSCHFELD: And it has to be  
22 something that is reviewed under that. So, even if  
23 it is active in non-small cell, the company has to  
24 request a marketing license for non-small cell in  
25 addition.

1 DR. SANTANA: Susan?

2 DR. WEINER: I guess part of what makes me  
3 so anxious about this conversation is that we  
4 started with the elegant statements of the  
5 accomplishments of the pediatric cooperative groups  
6 and now, suddenly, it is a question of mandating  
7 studies -- who is responsible for mandating studies  
8 of drugs that companies are proposing for other  
9 indications. I guess I just would like some  
10 reassurance that the relationship between the  
11 pediatric cooperative groups and the  
12 decision-making would be pretty seamless about  
13 this.

14 DR. SANTANA: I think both Malcolm and  
15 Steve can speak about that.

16 DR. SMITH: I would just second Susan's  
17 concern that I am not sure what the decision-making  
18 process will be, but whatever it is, there needs to  
19 be input from the research community about these  
20 decisions.

21 DR. SANTANA: Dr. Kaye?

22 DR. KAYE: It is sort of a semantic issue  
23 but another way of looking at the two principles  
24 just has to deal with our confidence in the level  
25 of evidence between the two. For instance, in the

1 sarcomas when you look at a rare, specific  
2 translocation it is such compelling evidence  
3 linking those diseases. On the other hand, every  
4 drug that comes out now, it seems to me, is going  
5 to have some mechanism of action because there is a  
6 big push for that. How you get the same confidence  
7 and the level of evidence that that is doing it, it  
8 is often intuitive and for a lot of the agents that  
9 are out there right now, that have been out there  
10 previously for the past couple of years there is a  
11 certain feeling, yes, it is probably not targeting  
12 what we initially thought it was. So, it is more  
13 likely, given the complexity of biology, that they  
14 may not be quite right on the mechanisms of these  
15 agents than being right. So, it is just something  
16 that you have to keep in mind. I think that is  
17 probably what is in the back of the mind -- you  
18 feel confident with the translocation when they  
19 come out with a tyrosine kinase inhibitor that says  
20 this is specifically what it is doing. I think our  
21 confidence this year is going to be not as great.  
22 It just brings in again, you know, empirical  
23 treatment. If I knew of a drug that was 80  
24 percent, 85 percent effective in small cell lung  
25 cancer I would certainly want to try it on any

1 disease, and that is sort of the empirical nature  
2 and I think there is a bandwagon right now on  
3 molecular targeting that is -- you know, I think  
4 the push for that has always been present. Those  
5 entities have always been present but there is a  
6 bandwagon that I think may be blinding us.

7 DR. HIRSCHFELD: Victor, I just want to  
8 say that the recommendations that would be useful  
9 would be to say, yes, the rule should be invoked;  
10 no, it should be waived; or we don't know yet and  
11 let's continue to examine this.

12 DR. SANTANA: I would vote for the latter.  
13 We don't know yet, and I think you have to take  
14 each case individually for these particular  
15 diseases.

16 DR. REYNOLDS: That is exactly what I was  
17 saying. If you recall my last slide, I didn't put  
18 on there I think that the Pediatric Rule should be  
19 invoked; I said that studies should be strongly  
20 considered. I think "by strongly considered" it  
21 means that we should gather a little more data in  
22 the process of doing this, and I think that is  
23 consistent with what you are saying. It is  
24 basically saying that if the targets are the same  
25 and if you can get the clinical data suggested,

1 then perhaps the Pediatric Rule might need to be  
2 invoked in this case.

3 DR. SANTANA: I think we have reached a  
4 consensus on that one. Does the agency feel that  
5 way?

6 DR. HIRSCHFELD: Right. I would like some  
7 clarification down the list, if there are any  
8 recommendations regarding waivers.

9 DR. SANTANA: Well, you know, I haven't  
10 treated or seen a lot of mesothelioma but I think  
11 they are probably the same disease. It is a  
12 pediatric disease but it is the same disease as in  
13 adults. That is what I was implying. I think the  
14 pediatric mesothelioma, as rare as it is, is  
15 probably the same disease as mesothelioma in  
16 adults. I am trying to answer the questions. I  
17 think probably the same is true with bronchiogenic  
18 tumors. With the exception we have had about small  
19 cell lung cancer, I think small cell lung cancer  
20 and non-small cell lung cancer are not pediatric  
21 disease and I don't want to go any further on that.

22 DR. PAZDUR: Let me just ask a technical  
23 question because I was unaware of the mesotheliomas  
24 and there are applications that we have looking at  
25 drugs for this disease. Are there sufficient

1 numbers of patients to even invoke this rule?

2 DR. SANTANA: I mean, in the whole history  
3 of St. Jude I think there have been ten patients.  
4 So, it is very, very rare. It is very rare.

5 DR. PARHAM: Very rare, five cases.

6 DR. SANTANA: How about endocrine tumors?  
7 We really didn't talk about those in the general  
8 context, but I would propose that thyroid carcinoma  
9 are probably the same diseases in adults as they  
10 are in kids. Anybody disagree with that comment?

11 [No response]

12 Then adrenal tumors other than  
13 neuroblastoma, Pat, do you want to comment on that?

14 DR. REYNOLDS: Well, I would suggest that  
15 fibrochromocytoma is probably the same regardless  
16 of its age.

17 DR. LINK: Except that that is a tumor  
18 that occurs in people who are progenitively  
19 predisposed.

20 DR. SANTANA: But when it gets manifested  
21 it is variable, as you well know. So, the  
22 pediatric disease is probably the same as in adults  
23 in terms of the genetics. It is just a matter of  
24 when it gets manifested.

25 Then, are there other pediatric

1 neuroendocrine tumors that have an adult  
2 counterpart that is not commonly classified as an  
3 adult neuroendocrine tumor but as some other type  
4 of adult malignancy such as a carcinoma? It is the  
5 same question as this morning which I had  
6 difficulty with. Anybody want to comment on that  
7 one? I can't think of any. David, any thoughts on  
8 that?

9 DR. PARHAM: I can't think of anything.

10 DR. SANTANA: Okay. Have we satisfied  
11 those questions for the agency? Let's go ahead and  
12 talk for the rest of the afternoon about the CNS  
13 malignancies. So, I invite Susan to come to the  
14 podium, and Dr. Burger is going to join us on the  
15 telephone. So, give us a second to get the  
16 telephone connection.

17 DR. BURGER: Hello.

18 DR. SANTANA: Dr. Burger, can you hear us?

19 DR. BURGER: Yes, I can.

20 DR. SANTANA: Welcome. For the purpose of  
21 the record, please state your name and your  
22 affiliation.

23 DR. BURGER: Yes, this is Peter C. Burger.  
24 I am from Johns Hopkins University, Department of  
25 Pathology.

1 DR. SANTANA: Thanks, Peter. We are going  
2 to have two short presentations, one by Susan and  
3 one by Howard, and we are just going to go ahead  
4 and do the presentations and then we will open up  
5 for discussion. Okay?

6 DR. BURGER: Fine.

7 DR. SANTANA: Susan?

8 Perspectives on CNS Malignancies

9 DR. STAUGAITIS: Thank you.

10 [Slide]

11 I am going to give some of my perspectives  
12 on CNS malignancy, and I will be reiterating many  
13 of the points that were brought up already today  
14 and I will emphasize some of the unique opinions  
15 that I may have compared to the rest of the group.

16 [Slide]

17 The background that I come from is as a  
18 neurobiologist with an interest in development and  
19 also as a neuropathologist. I do not have the  
20 breadth of experience as my colleagues, like Dr.  
21 Burger, in terms of how much I have seen in CNS  
22 malignancies, neither am I an oncologist, and I  
23 have been encouraged to speculate to provoke  
24 discussion and so as a disclaimer in the beginning,  
25 I want to say that I am going to throw out a lot of

1 crazy ideas. These are not recommendations; they  
2 are for my clinical colleagues to respond to and  
3 determine whether or not they have any weight.

4 I am going to talk about CNS neoplasms by  
5 reshuffling the deck in different ways. First, I  
6 will go through the classical dogma of the general  
7 classification of tumors as defined by histology,  
8 then I will describe them in other ways, group them  
9 in other ways as defined by physiology, for  
10 example.

11 [Slide]

12 Just for some background, the diagnosis of  
13 brain tumors is very different now than it was many  
14 years ago. Imaging has enabled us to identify  
15 smaller lesions, subclinical lesions. Biopsies are  
16 smaller. And, if we are talking about whether  
17 different malignancies are the same, a  
18 neuropathologist often wonders whether the tumor is  
19 the same when they are two centimeters apart from  
20 each other in the same patient.

21 One of our roles is in terms of specimen  
22 adequacy, and one of the issues that was brought up  
23 earlier in terms of can we do all of the genetic  
24 studies that we would like to do on the tissue that  
25 we are provided, and sometimes that is just not

1 possible, although we would like to be able to  
2 obtain as much tissue as we can.

3           Classically, the neuropathologist looks at  
4 tumors from the point of view of histologic  
5 phenotype and also grade and, as we have mentioned  
6 throughout the day, we have additional information  
7 in terms of gene expression. Immunocytochemistry  
8 is now a standard of care in pathology in general,  
9 and genomic alterations and molecular diagnosis is  
10 on its way there.

11           [Slide]

12           One of the things that the pathologist  
13 contributes with these molecular studies is that it  
14 is up to us to tell the molecular biologist where  
15 the tumor is and what to sample. I don't want  
16 anybody to really lose sight of that aspect of our  
17 responsibility.

18           The morphologic classification of CNS  
19 neoplasms is based upon a resemblance of neoplastic  
20 cells to normal cells. Throughout the ages people  
21 have used this to infer a cell of origin. I am  
22 very hesitant to say that. I will basically be  
23 talking about the phenotypes of different cells,  
24 not necessarily the specific cell that neoplasm  
25 might be derived from because I think that we

1 probably don't know all of that information.

2           And, the cell of origin is important  
3 because this becomes the basis of in vitro  
4 experimental models on which initial compounds are  
5 tested. So, for example, do mature human adult  
6 astrocytes in culture represent a model for all  
7 kinds of astrocytomas? I am not completely sure.  
8 There could be progenitors, other kinds of  
9 precursor cells that may reflect the physiology of  
10 the cell that becomes transformed.

11           [Slide]

12           In terms of just outlining the different  
13 tumors, I am going to describe them in terms of  
14 their sites of origin, CNS parenchymal accessory  
15 structures and the CNS coverings. The largest  
16 group are the CNS parenchymal neoplasms and, as I  
17 alluded to earlier, I am dividing this into cells  
18 with a glial phenotype, a neuronal phenotype and an  
19 embryonal phenotype.

20           Among the glial phenotype astrocytomas,  
21 oligodendrogliomas, the neoplasms look like the  
22 normal cells in many of the instances but it does  
23 not necessarily imply a cell of origin.

24           Astrocytomas tend to have a high  
25 propensity to progress to higher grade lesions,

1    whereas with some of the other neoplasms --  
2    oligodendrogliomas -- we can have a higher grade  
3    progression to that although it is less likely. In  
4    ependymoma cytologic malignancy often is not  
5    correlated with the clinical behavior on the  
6    patient. So, even within this classification there  
7    are many differences.

8                   [Slide]

9                   The neoplasms with the neuronal phenotypes  
10    tend to be more within the pediatric population.  
11    They tend to be more low grade, and the most common  
12    of these are the ganglioma/gangliocytoma family.  
13    The other neoplasms with names like neurocytoma,  
14    dysembryoplastic neuroepithelial tumor lead us to  
15    say that we really don't know what we are talking  
16    about with these lesions. They express certain  
17    antigenic phenotypes that make us infer that they  
18    might have properties of neurons or neuron-like  
19    cells or progenitor-like cells, but there is still  
20    a lot to be learned about these. Fortunately, many  
21    of these are very benign lesions and often not an  
22    issue for drug development.

23                   [Slide]

24                   The third category are the embryonal  
25    neoplasms, such as medulloblastoma, the

1 supratentorial PNET tumors and the atypical  
2 teratoid/rhabdoid tumor.

3 [Slide]

4 The accessory CNS structures include the  
5 lesions of choroid plexus, the pineal gland and  
6 pituitary.

7 [Slide]

8 The lesions arising in the coverings  
9 include the meningeal tumors such as meningiomas,  
10 hemangiopericytoma, other sarcomas and melanocytic  
11 neoplasms, as well as the peripheral nerve sheath  
12 tumors.

13 [Slide]

14 Now I would like to rearrange these in  
15 terms of who gets what. For the most part,  
16 virtually every age patient can get these different  
17 CNS tumors but some are much more commonly found in  
18 adults; some more commonly found in pediatrics; and  
19 some are almost exclusively pediatric.

20 [Slide]

21 For example, most gliomas are found to a  
22 much greater extent in adults. Histologically, to  
23 my knowledge, the fibrillary gliomas in adults and  
24 the pediatric population histologically are  
25 essentially the same. So, perhaps they could be

1 treated as the same.

2           Similarly, for the other neoplasms that I  
3 list here, the pineal parenchymal neoplasms, the  
4 embryonal pineal blastoma are more common in  
5 younger people but histologically the tumors are  
6 the same. Similar, for the tumors of the  
7 coverings.

8           [Slide]

9           In terms of pediatric being much greater  
10 than adult, we have the unusual low grade  
11 astrocytoma, such as pilocytic astrocytoma and  
12 pleomorphic xanthoastrocytoma, the intraventricular  
13 ependymoma, the glial and glial neuronal neoplasms  
14 and the embryonal neoplasms, such as  
15 medulloblastoma and, as you can see on the slide,  
16 choroid plexus, germ cell and craniopharyngioma.  
17 These are the ones where I think we really have to  
18 try and find criteria for including this with other  
19 neoplasms because it is unlikely that drugs would  
20 be developed specifically for these, given that  
21 there are small populations of people who are  
22 actually affected.

23           [Slide]

24           Finally, there are a few neoplasms that  
25 are virtually unheard of in adults, such as the

1 desmoplastic infantile astrocytoma or ganglioma,  
2 atypical teratoid/rhabdoid and supratentorial PNET.

3 [Slide]

4 We mentioned a lot about the effect of  
5 mutations and alterations, and I want to take a  
6 moment to think about what the genetic alterations  
7 that we can detect mean in terms of the biology of  
8 the tumor. For example, a mutation or  
9 rearrangement affects a specific gene in a specific  
10 way and we can see how it is reflected in gene  
11 expression. Whereas, a gain or a loss of genetic  
12 material can involve huge areas of the chromosome  
13 and it may be difficult to predict the behavior or  
14 the responsiveness of a therapy based on loss of  
15 chromosome 1P because, for example, loss of  
16 chromosome 1P in an oligodendroglioma may have a  
17 different effect on a tumor than a loss of  
18 chromosome 1P in a neuroblastoma, and so forth.

19 [Slide]

20 In thinking about the cell of origin of  
21 the neoplasm is does the physiology of the  
22 precursor cell that is transform affect the  
23 behavior of the neoplasm, and does that affect the  
24 way that drugs interact with it? For example, once  
25 a precursor cell is transformed by genetic

1 alteration, do its normal physiologic processes  
2 matter or don't they? Is it important to think  
3 about the cell of origin at all?

4 I think with higher grade tumors that  
5 acquire more and more mutations, that becomes less  
6 important. The low grade, these elusive tumors  
7 where we don't have specific molecular markers for  
8 early intervention, those tumors may actually have  
9 more of a relationship to the precursor cell.

10 [Slide]

11 Another thing that I would like to  
12 consider in my talk is the relationship of familial  
13 syndromes that are associated with CNS neoplasms.  
14 Many of the neoplasms, such as the astrocytomas and  
15 the meningiomas that one sees in the pediatric  
16 populations are superimposed on a genetic syndrome.  
17 As you can see from the different syndromes that  
18 are listed here, some tumors are increased in  
19 incidence on very different genetic backgrounds.  
20 For example, astrocytomas have been associated with  
21 neurofibromatosis Type 1, neurofibromatosis Type 2  
22 with the Li-Fraumeni syndrome in TP53 alterations,  
23 with APC mutations. Are all of these tumors the  
24 same? Histologically they look identical but  
25 because potentially different pathways are involved

1 and this is the substrate upon which these tumors  
2 are superimposed, can we really make predictions as  
3 to whether the indications are the same?

4 [Slide]

5 Let me reshuffle the deck again a little  
6 bit more. We talked about histopathology. What  
7 about the growth properties of transformed cells?  
8 Can we lump histologically disparate tumors  
9 together based upon, say, proliferation, survival,  
10 migration, motility and angiogenesis? I would just  
11 like to throw out a few examples here for  
12 discussion.

13 For example, some of the rare, highly  
14 malignant tumors that are very common in the  
15 pediatric populations such as medulloblastoma, the  
16 other PNETs and high grade gliomas, choroid plexus  
17 carcinomas are rapidly dividing tumors and the  
18 strategy in oncology for years has been just to  
19 target the rapidly proliferating cells. If we can  
20 identify specific molecular targets that interfere  
21 with a particular aspect of the cell cycle, that  
22 could be effective and less toxic and that is  
23 advantageous. But this is sort of an approach  
24 where we are lumping together tumors based upon  
25 their growth properties, and I think it also ties

1 in with the comments that were made earlier about  
2 grade.

3 [Slide]

4 Another way that we might be able to link  
5 neoplasms is in terms of their ability to  
6 infiltrate into the central nervous system. One of  
7 the aspects of CNS malignancies that make them  
8 really refractory to treatment is the ability of  
9 single cells to migrate long distances, and if  
10 there was an agent that could interfere with the  
11 motility of one type of transformed glial cell,  
12 might it also be able to interfere with the  
13 motility of another type of transformed glial cell?

14 Similarly, if one were developing  
15 mechanisms by which therapies can home to tumor  
16 cells that infiltrate widely, perhaps that can be  
17 applied to many classes of neoplasms.

18 [Slide]

19 Another example would be angiogenesis  
20 inhibitors. For example, both high grade  
21 astrocytomas, such as glioblastoma multiforme and  
22 low grade pilocytic astrocytomas, show  
23 histologically similar vascular proliferation  
24 patterns. Do the same mechanisms promote this  
25 proliferation and, if so, can drugs designed to

1 target the vasculature in high grade astrocytomas  
2 be effective in unresectable pilocytic  
3 astrocytomas? A pilocytic astrocytoma resected  
4 from the cerebellum is essentially cured but there  
5 are many, many patients who have very deep lesions  
6 around the hypothalamus that can not be adequately  
7 resected and the vascular proliferation that is  
8 associated with these neoplasms may be a target for  
9 therapy and extending the rule.

10 [Slide]

11 We have mentioned p53 mutations a number  
12 of times and I will just reiterate some of the same  
13 points. Many, many of the neoplasms in the CNS  
14 have mutations in p53. One thought is to find  
15 agents that will stimulate the function of p53. On  
16 the other hand, there are also agents being tested  
17 that will inhibit the function of p53 in normal  
18 cells so that normal tissues can be protected  
19 against the genotoxic stress of therapies. This  
20 may be particularly important to test in the  
21 pediatric population where we are very concerned  
22 about the developing nervous system and the effect  
23 that different radiotherapies and chemotherapies  
24 can have. So, I think we have to keep our minds  
25 open and also think about agents that protect the

1 normal tissues.

2 [Slide]

3 We have mentioned the PDGF receptors many  
4 times already today. There is evidence that  
5 PDGF-alpha receptors are overexpressed in a number  
6 of gliomas, including fibrillary astrocytoma,  
7 oligodendroglioma, ependymoma and pilocytic  
8 astrocytoma. If it can be shown that the  
9 expression of this receptor and the activity of  
10 this receptor and pathway is critical to the  
11 neoplastic phenotype, I would agree with what we  
12 have already said before, that it could be an  
13 indication to become more inclusive of the types of  
14 neoplasms that are indicated for these agents.

15 [Slide]

16 On the other hand, let's think about the  
17 epidermal growth factor receptor where, in adults,  
18 de novo glioblastomas tend to be amplified;  
19 secondary glioblastomas do not. Are they different  
20 tumors? And, how do you define an indication for  
21 something that has activity on the epidermal growth  
22 factor receptor or its downstream pathway, and what  
23 neoplasms should you extend these drugs to or limit  
24 them to?

25 [Slide]

1           Finally, I think that others today have  
2 emphasized that it is important to look at the  
3 entire pathway. When I first started to read about  
4 the genetics of neoplasms I was always a little bit  
5 discouraged when I would learn that, well, 20  
6 percent of these tumors have this alteration and 5  
7 percent of these tumors have another alteration,  
8 but as we learn more about the intracellular  
9 signaling mechanisms and how pathways can come  
10 together, and we put together the alterations  
11 within pathways we will get up to numbers like 60  
12 percent and 70 percent and 80 percent of neoplasms  
13 involve a particular pathway. Then, the rational  
14 biologic approach would be to find the bottleneck  
15 in that pathway and see if there are ways to  
16 inhibit or activate that.

17           [Slide]

18           Finally, I will just tone myself down a  
19 little bit and express a few cautions that I  
20 considered that while I was putting together my  
21 thoughts on this presentation. The central nervous  
22 system is very different than the other parts of  
23 the body in that it is encased in our hard skulls,  
24 and the necrosis and swelling that are associated  
25 with rapid and efficient cell killing may have

1 truly adverse effects within the confines of the  
2 central nervous system.

3           Environmental signals that may affect the  
4 behavior of neoplastic cells may change during the  
5 development. Specific targeted therapies will work  
6 only if the inhibited pathway is intact in the  
7 particular tumor being treated.

8           I just read a paper in Science regarding  
9 the treatment of CML with STI571, and apparently  
10 there is a population of populations who, after  
11 responding to the therapy, become refractory and it  
12 was identified that these patients have acquired a  
13 mutation that makes the cells resistant to this  
14 particular gene. They further proved that the  
15 activity was still important in the malignant  
16 behavior of this particular neoplasm. So, I think  
17 in all of our discussions we have to remember that  
18 neoplasms are constantly changing, constantly  
19 evolving processes that may always be one step  
20 ahead of us.

21           Then, finally, therapies that target  
22 specific functions, such as proliferation,  
23 migration, may actually adversely affect the normal  
24 developing cells within the nervous system and that  
25 changes rapidly, especially in early childhood, and

1 may actually be reasons to invoke the waiver in  
2 this. With that, I would like to thank you.

3 DR. SANTANA: I would like to invite  
4 Howard to come to the podium.

5 Perspectives on CNS Malignancies: Clinical Aspects

6 DR. FINE: I want to thank the organizers  
7 who asked me to speak here. After Henry did his  
8 usual nice job and Susan spoke about the science,  
9 which is always one of my favorite topics, the  
10 question is what can I say here? Probably not  
11 much.

12 [Slide]

13 But what Steve suggested I talk to the  
14 group about -- obviously, there are some world  
15 renowned oncologists around the table but many of  
16 you are not so involved in neuro-oncology and brain  
17 tumors. So, he thought it would be useful for me  
18 to just go over some of the basic clinical aspects  
19 as far as how these patients do, the natural  
20 history of their disease clinically speaking, how  
21 we approach them, how we treat them and some  
22 general outcomes that we expect from these tumors.  
23 So, I thought I would do that. So, I don't think I  
24 need this as an introduction. Suffice it to say  
25 that these are an important group of tumors both in

1 the adult and the pediatric population, and  
2 increasingly more an important group of tumors than  
3 I think was ever appreciated. Certainly, I can  
4 tell you that at the National Cancer Institute, on  
5 a national level, this group of tumors is  
6 increasingly being recognized as a very important  
7 target for the next decade.

8           Along with the problem of these tumors  
9 causing a significant amount of cancer mortality is  
10 the morbidity that both adults, and in particular  
11 the children, suffer st these tumors, not just from  
12 the tumors themselves but from the treatments that  
13 we use to treat them. I think whenever we talk  
14 about brain tumors in either the pediatric or the  
15 adult population, we have to think about toxicity  
16 in a very different way than we do for systemic  
17 tumors because the toxicity is almost permanent and  
18 it is always a balancing act in trying to decide  
19 whether a few months of increased life is really  
20 worth significantly decreased quality of life.

21           [Slide]

22           I think when we talk about the pediatric  
23 role, at least when I think about it, I think of a  
24 couple of questions. Number one, are the tumor  
25 types the same? And,; is a specific tumor type the

1 same in a child compared to an adult? I think  
2 there are several ways that we can answer that, and  
3 we have already addressed those ways in the other  
4 tumor types.

5           There are obviously the biologic criteria,  
6 and Susan and Henry have both kind of addressed  
7 that, both as far as standard pathology is  
8 concerned, as well as molecular diagnostics. But  
9 the other way to address that is the clinically  
10 behavior of the tumor, both as far as the natural  
11 history of the tumor and how the tumor responds to  
12 therapy. As I said, that is what I will try to  
13 address over the next five or ten minutes here.

14           [Slide]

15           Again, we have seen this slide before, or  
16 variations of this slide, relative to the first  
17 question I asked, are the tumors the same? Well,  
18 the tumors are the same except their distribution  
19 is highly different between adults and children,  
20 with actually by far the most common adult brain  
21 tumor being metastatic tumor, something we actually  
22 forget about sometimes, with high grade gliomas  
23 being by far the most common problem after that.  
24 With pediatric tumors we are really dealing with  
25 embryonal tumors and then low grade gliomas as

1 opposed to the high grade gliomas.

2           I am sure you don't want to hear me go  
3 through the natural history and treatments of all  
4 the 75 different subtypes, or whatever the most  
5 recent WHO categorization tells us the subtypes of  
6 CNS tumors are, I thought probably the most  
7 important -- and I asked Steve who agreed -- the  
8 most important tumor to go over is gliomas. The  
9 reason I say that is that although gliomas are not  
10 the most common pediatric brain tumor, the fact of  
11 the matter is, and we can and should open this up  
12 for discussion after this talk but most of the  
13 other brain tumors that we see in children are  
14 hardly represented at all in adults. So, for this  
15 discussion of the Pediatric Rule, it is unlikely  
16 that a drug company is going to design a drug for  
17 cranial pharyngiomas in adults where we are going  
18 to have to worry applying the Pediatric Rule.

19           So, to keep this on a practical side, and  
20 we can change that if you want but to keep it on a  
21 practical side, the reality is if drug companies  
22 are going to develop a drug at all for tumors, and  
23 that is another issue but the few times they do, it  
24 is going to be for gliomas because that is the  
25 disease in adults and that is where I think we need

1 to address the issue of the Pediatric Rule, at  
2 least in my personal opinion.

3 [Slide]

4 So, the first thing -- and you can quote  
5 me on this; the reference is down below. It is my  
6 anticipation this will be a truism that goes on for  
7 years.

8 DR. SANTANA: It won't be dinosaurs  
9 anymore or rainbows; it will be something else!

10 DR. FINE: But I think this is important.  
11 A glioma is not a glioma; it is a heterogeneous  
12 group of diseases and, as a matter of fact, it is a  
13 heterogeneous disease even within a patient. So,  
14 you know, Henry showed some data and Susan showed  
15 some data that say that some of the molecular  
16 alterations in the pediatric high grade gliomas do  
17 not exactly correlate with those of the adult  
18 patients and it is important to understand that  
19 within the adult patients the genetic alterations  
20 are hugely variable. Whether that reflects the  
21 fact that they are many, many different  
22 subcategories at a genetic expression profile level  
23 of gliomas, whether that reflects the fact that  
24 these tumors, as opposed to leukemias for instance  
25 or even pediatric sarcomas, genetically messed up

1 tumors -- these tumors are highly aneuploid and  
2 what genetic alterations are really important for  
3 the pathogenesis of these diseases is not yet  
4 clear. So, I think we have to be very careful  
5 about over-reading the genetics that we find in  
6 these tumors for now until we really understand who  
7 the important players are. That, again, gets back  
8 to what I keep talking about today, validation of  
9 molecular targets.

10 [Slide]

11 So, let's first talk about the two major  
12 categories using standard pathology criteria of  
13 gliomas, those being low grade gliomas -- generally  
14 if we talk about a four-tier scale like the WHO,  
15 grade 1 and 2 gliomas, and high grade gliomas,  
16 grades 3 and 4, variously known as anaplastic  
17 astrocytomas and glioblastomas.

18 To contrast the natural history of low  
19 grade gliomas and, please, with Roger and Henry and  
20 Larry, world renowned pediatric neuro-oncologists  
21 here, feel free to correct anything you see on the  
22 slide but generally speaking, the natural history  
23 in adults -- generally these tumors are limited to  
24 astrocytic or oligodendroglioma histologic subtypes  
25 or mixed histologic subtypes. While in children we

1 get multiple subtypes, and we have already heard  
2 about that from the pilocytic astrocytoma to the  
3 ependymal tumors to mixed neural glial types of  
4 subtypes. So, that is one way that they are  
5 different.

6           Certainly, in adult these are slowly  
7 progressive and infiltrative tumors and that is  
8 generally true for low grade tumors in children but  
9 not always. Some of these tumors appear to be  
10 self-contained. Certainly the pilocytic tumors  
11 are, and they can be cured if they can be safely  
12 surgically resected, something we really don't find  
13 on the adult side. So, I think that is a key  
14 difference.

15           Another very important biologic difference  
16 is that most patients or almost all adults with low  
17 grade tumors die of their tumors. These are not  
18 benign tumors, and the way the majority of patients  
19 die of low grade tumors is that they transform to  
20 high grade tumors, at least about 60-80 percent of  
21 them. That number, although it is very difficult  
22 to come by, in the pediatric population is much  
23 smaller. So, that reflects an important biologic  
24 difference, at least in my mind, between these two  
25 different subtypes.

1           Again, I think this is also reflected in  
2 the survival. Again, why I never like to use and  
3 would never use the word "benign" tumor for a low  
4 grade glioma in an adult is that the ten-year  
5 survival rate is well less than 30 percent, and  
6 since most adults who get low grade gliomas tend to  
7 be younger adults, that is not a benign disease.  
8 Also, it should be noted that there appears to be  
9 no survival difference depending on anatomic  
10 location of the tumor.

11           These numbers and these facts contrast  
12 with what we generally see in pediatric low grade  
13 gliomas where the ten-year survival is probably  
14 well over 50 or 60 percent, and that survival, as  
15 Roger went over with me very clearly last night, is  
16 very much dependent on location of the tumor.  
17 Whether that reflects the surgical resectability of  
18 the tumor or whether that reflects something about  
19 the natural history and biology of the tumor I  
20 think remains unclear at this point.

21           [Slide]

22           As far as how do we approach adults and  
23 children with low grade gliomas, well, I think for  
24 both these tumors if they can be surgically  
25 resected, it is considered optimal. Certainly,

1 more so in adults. When we can't resect them  
2 fully, or even if we can, usually that is not  
3 enough and, as a matter of fact, it is almost never  
4 enough with the exception of maybe truly low grade  
5 oligodendrogliomas. Therefore, radiation therapy  
6 is commonly used. There still is a big question  
7 about the timing of radiation therapy -- radiate me  
8 now or radiate me later, meaning at the time of  
9 tumor progression. That remains an unknown issue.

10           Although long-term toxicity of radiation  
11 to adults remains a problem that we talk about, it  
12 isn't one of the major, major issues as it is, as  
13 we will talk about, in children. There is a  
14 question, increasingly so, of the use of focal  
15 radiotherapy for low grade gliomas. Chemotherapy  
16 has no proven benefit in the treatment of low grade  
17 gliomas. There is increasing evidence to suggest  
18 that maybe low grade oligodendrogliomas,  
19 particularly with the 1P, 19Q marker, may have  
20 sensitivity to alkylating agents, and maybe even  
21 mixed gliomas may have some activity though, again,  
22 I think that remains to be seen as far as how  
23 common that is.

24           As far as children are concerned, again,  
25 if we can fully resect most of these tumors,

1 certainly tumors like pilocytics, that is  
2 considered optimal treatment. We are very  
3 hesitant, because of the toxicity associated with  
4 radiation, to use radiation and it is often, as  
5 opposed to second-line therapy, a last choice. One  
6 of the reasons it is our last choice is because,  
7 indeed, chemotherapy can be quite effective in  
8 these tumors, as opposed to adults, with  
9 carboplatinum or platinum-based regimens, having  
10 the potential to give quite high response rates and  
11 control these tumors for a number of years.

12           So, I think there are significant  
13 differences in the natural history of low grade  
14 gliomas in adults and children. Whether that  
15 should affect the Pediatric Rule is something that  
16 I am going to throw open to the committee.

17           [Slide]

18           Let's talk about high grade tumors. Most  
19 commonly in adults they are supratentorial as  
20 opposed to in children where we are dealing with  
21 basically almost an equal split of infratentorial  
22 versus supratentorial. Both these tumors, however,  
23 whether they be in adults or children, are bad  
24 tumors. They are infiltrative. They are rapidly  
25 progressive. They are destructive. They have high

1 degrees of angiogenesis. They disrupt the  
2 blood-brain barrier and the prognosis is poor.

3           The prognostic variables that we know for  
4 high grade gliomas over the years, shown by  
5 multiple studies, many done by Victor Levin who is  
6 here today, include very powerful predictors such  
7 as age, grade, performance status of patients and  
8 the postoperative radiographic residual tumor.  
9 That is not to say the extent of resection. The  
10 only thing that has been shown is that when you  
11 measure radiographically the amount of tumor left  
12 after surgery, that is a predictor of survival.  
13 Surgeons like to translate this to say, oh, that  
14 means we should take more out and whether that is  
15 true or not is not necessarily the case.

16           Prognosis for children with high grade  
17 gliomas also is clearly grave, meaning an  
18 anaplastic astrocytoma versus a glioblastoma is a  
19 very clear predictor. It appears that  
20 postoperative radiographic tumor extent is also a  
21 prognostic variable. Performance status is harder  
22 to judge in children, as you all know well, and age  
23 as far as small children versus teenagers is  
24 something that I think is also less clear.

25           [Slide]

1           When we talk about treatment of high grade  
2 gliomas, surgery is uniformly, I think it is fair  
3 to say, considered important at least as far as  
4 surgery for determining a diagnosis. I think as of  
5 the year 2001, we want a histologic diagnosis on  
6 almost everyone. Probably two exceptions to this  
7 are patients with infiltrating brain stem lesions  
8 where radiographically it can almost be nothing  
9 else, and morbidity of biopsy of this area makes  
10 the risk versus benefit ratio against doing the  
11 surgery. Then, there is a cohort of patients who  
12 have prototypic radiographic criteria of  
13 glioblastoma who are basically morbid from their  
14 tumors, for whom we know the treatment isn't going  
15 to do anything for them and some of those patients'  
16 families elect not to have biopsies.

17           Generally speaking, although it remains  
18 controversial, for most of the major brain tumors  
19 it is generally thought, when possible, maximal  
20 debulking surgery is advantageous for high grade  
21 gliomas, mainly for the purposes of diminishing the  
22 mass effect from these large tumors, for the  
23 purposes of decreasing steroid requirement over the  
24 next several months. It also decreases the  
25 potential sampling bias because, as we have talked,

1 these are highly heterogeneous tumors from one area  
2 to another. Although, again, the trial hasn't been  
3 and will never be done, that being a randomized  
4 trial of biopsy versus surgery, I think most people  
5 believe that surgery probably extends survival at  
6 least to some extent, though probably not hugely.

7           Larry Kun is here who has irradiated more  
8 children with brain tumors probably than anyone  
9 else in the world. I would like to hear his  
10 comments but, generally speaking, radiation is  
11 still the gold standard for high grade gliomas in  
12 both adults and children.

13           Involved field radiation therapy is now  
14 standard as opposed to whole brain radiation,  
15 thereby potentially decreasing or definitely  
16 decreasing the neurocognitive toxicities of  
17 radiation. Generally we are talking about  
18 something in the range of 5940 or 6000 centigrade  
19 spread out over 30-33 fractions. Different dose  
20 and fractionation schemes have been looked at  
21 continuously through the RTOG and other  
22 organizations. They continue to be looked at but  
23 to this point there has been no dose or  
24 fractionation scheme that has clearly been shown to  
25 be superior over the standard regimen that I just

1 spoke of before. There is a question of the use of  
2 high dose focal radiation techniques, like  
3 radiosurgery, a gamma knife and so forth though its  
4 role remains to be defined.

5           Then, again, toxicity as far as the acute  
6 toxicity of radiation, meaning over the first few  
7 months, is generally one related to radiation  
8 necrosis. The real toxicity we are concerned  
9 about, particularly in children, of course, are the  
10 long-term, well-documented neurocognitive  
11 dysfunctions that appear to be dose and extent of  
12 CNS related, as well as the age at which the  
13 patient was radiated at.

14           [Slide]

15           How about chemotherapy? Well, I think of  
16 chemotherapy in two roles, first as part of the  
17 initial treatment or adjuvant treatment -- I don't  
18 really like to use the term "adjuvant" because at  
19 least on the adult side when we think of adjuvant  
20 we think of breast cancer when the tumor has been  
21 fully removed. These tumors are never fully  
22 removed but at least as far as up-front treatment,  
23 what is the role of chemotherapy? It is  
24 controversial. There have been multiple randomized  
25 trials. The results are mixed. The reasons that

1 the results are mixed, in my opinion, is that most  
2 of these trials consist of patients that are hugely  
3 heterogeneous in their prognostic factors as well  
4 as their tumor types, and most of the trials have  
5 been underpowered to detect subgroup analysis  
6 difference.

7           We have performed a meta-analysis. There  
8 has now been another meta-analysis that has looked  
9 at the use of adjuvant chemotherapy. We and the  
10 other group have shown that there appears to be a  
11 survival advantage for the use of chemotherapy in  
12 adults in patients with anaplastic astrocytomas,  
13 with the best regimen appearing to be a regimen  
14 developed by Victor, PCV, though there is some new  
15 retrospective data from RTOG and UCSF that suggests  
16 that single agent nitrosourea may be as good as PCV  
17 in adjuvant treatment, and now there is the new  
18 drug, just approved by the FDA about a year ago,  
19 tenozolamide. Its role as up-front treatment is  
20 being explored at a number of centers.

21           The question of the role of chemotherapy  
22 for the more common glioblastoma remains  
23 controversial. Our meta-analysis suggested that  
24 there was a very minimal benefit. The benefit that  
25 did exist appeared to have benefit in the patients

1 with the best prognostic factors, which is only  
2 about 10-20 percent of all patients. So, the  
3 majority of patients did not appear to benefit.  
4 Whether patients get chemotherapy up front or not  
5 remains a controversial area and is very physician  
6 dependent, I think it is fair to say, in this  
7 country.

8 Children with glioblastoma appear to have  
9 somewhat of a survival advantage when they use  
10 chemotherapy, though it is less clear that children  
11 with anaplastic gliomas benefit all that much when  
12 up-front chemotherapy is given.

13 [Slide]

14 When we look at chemotherapy for recurrent  
15 gliomas, there have been few agents with documented  
16 objective responses. Temozolamide, as I mentioned  
17 before, is the most recent of those and, outside of  
18 that, the FDA, not counting Gliadel, I don't think  
19 has approved a drug for glioma in 30 years, since  
20 BCNU, and I think there is a reason for that and it  
21 is not a political reason; it is a biology reason.

22 There are a few agents with proven  
23 improvements in quality of life, and there are few  
24 agents, maybe zero, with documented improved  
25 survival with, again, the exception possibly of the

1 Gliadel wafer and that benefit, if it exists, is  
2 marginal.

3 [Slide]

4 Basically, the treatment outcome for low  
5 grade gliomas in adults is quite poor. In children  
6 it can be good with the exceptions of the subtypes  
7 we talked about. For adults the treatment of high  
8 grade gliomas is horrible and it is absolutely no  
9 better in children.

10 [Slide]

11 So, points to consider for discussion -- I  
12 think a couple of things. Number one, clinical  
13 differences in natural history of high grade  
14 gliomas between adults and children appear to be  
15 trivial, in my opinion. Potentially promising  
16 agents for which there are drugs now being tested  
17 in the adults include drugs that are targeting the  
18 EGFR, PDGF pathways, PI3 kinase, the AKT,  
19 angiogenic targets such as VEGF or its tyrosine  
20 kinase high affinity receptor, FLK, and certainly  
21 the P16/RB E2F pathway all are promising targets  
22 that are being looked at in adults, and I see no  
23 reason why children with high grade gliomas  
24 shouldn't be given the opportunity to explore these  
25 promising new drugs.

1           I do have to say the caveat, which I put  
2   on the bottom of this slide, which I mentioned  
3   earlier today. I think it is worth considering  
4   what do we do if drug X that targets, for instance,  
5   the variable deleted EGFR which is so common in  
6   adult gliomas but is not found in pediatric gliomas  
7   is being developed for adult gliomas? Do we invoke  
8   the Pediatric Rule there? So, again, this drug is  
9   being developed for high grade gliomas but there is  
10  a specific target that we don't actually find on  
11  the high grade gliomas in children. What do we do  
12  with that drug?

13           [Slide]

14           As final points to consider, low grade  
15  gliomas in children do appear to constitute a  
16  heterogeneous group of diseases, many of which  
17  appear to be different than adult low grade gliomas  
18  both in their natural history and in the response  
19  to therapy. So, what do we do here? Should they  
20  be treated the same? As I also mentioned, should a  
21  drug with modest benefit in survival, if one is  
22  identified for adults for instance, but with  
23  significant long-term neurotoxicity be considered  
24  similarly in the pediatric population, given the  
25  fact that we expect the child to more likely live a



1 committee. That is, if a sponsor is coming forth  
2 with the example you gave, drug or biologic X that  
3 targets a specific receptor, for example, the case  
4 he gave, but in pediatrics we have the same  
5 histologic disease but the receptor is not  
6 expressed, would the rule be invoked in that  
7 scenario? I would like to follow up on that as a  
8 point of discussion. Anybody want to comment on  
9 it? Victor?

10 DR. LEVIN: I think it is a non-issue.  
11 The real question is, is it a target in either case  
12 and there are other EGF receptor kinase inhibitors;  
13 there are antibodies. There are all sorts of  
14 different approaches that one can validate that  
15 that is a logical target for a lower grade  
16 astrocytic tumor. So, I was perplexed by the  
17 question because, to me, it was not an issue.

18 DR. FINE: That was just an example.  
19 Clearly there are going to be -- not clearly, there  
20 are likely to be things identified on adult gliomas  
21 that are validated to be targets that aren't at  
22 least obviously there, or may not obviously be  
23 there in pediatrics. So, forget about how you feel  
24 about the variable EGFR receptor but use it  
25 hypothetically as a target that exists on a high

1 grade glioma in adult that doesn't exist in a high  
2 grade glioma in pediatrics. The question is what  
3 do you do with that as far as the Pediatric Rule is  
4 concerned?

5 DR. LEVIN: It is the same issue. If it  
6 doesn't exist, then maybe it is not as important a  
7 target or, in the adult maybe it is not even a  
8 target, just an abnormality that is seen. Just  
9 because you see an abnormality it doesn't mean it  
10 is a target.

11 DR. FINE: That still gets back to the  
12 validation. You are arguing that all validated  
13 targets in adult tumors will be found in pediatric  
14 tumors.

15 DR. LEVIN: No, I would say that all  
16 validated targets in the spectrum of astrocytoma  
17 should be validated targets in the spectrum of  
18 astrocytoma no matter what age, maybe excluding  
19 under one, but within reasonable limits they are  
20 going to be similar.

21 DR. FINE: So, that reflects your bias  
22 that these tumors are exactly the same.

23 DR. LEVIN: I think these tumors are more  
24 similar than different --

25 DR. FINE: I agree.

1           DR. LEVIN:  -- and I am not quite sure  
2   that the reason that we don't see response -- that  
3   biologically as patients get older the response  
4   deteriorates isn't more a reflection of how little  
5   we have to offer and it may basically reflect the  
6   fact that we are using toxins and older patient  
7   deals with DNA damage much differently than a young  
8   person.  I mean, there are a lot of different  
9   reasons for failure of our therapy besides the  
10  difference in tumor generating targets.

11           DR. KUN:  And, both in pediatrics and  
12  adults these tumors are very heterogeneous, as you  
13  know, and the difficulty with trying to make a  
14  blanket statement, particularly for the high grade  
15  gliomas in pediatrics, is that there are subsets  
16  that seem to track more akin to adult tumors  
17  biologically and others that don't.  So, I don't  
18  think you can make that as a blanket statement.

19           DR. SANTANA:  Amar?

20           DR. GAJJAR:  Another practical point is  
21  validating targets in pediatric oncology is going  
22  to be very difficult.  I mean, to subject a child  
23  who is on one of these target derived therapies to  
24  biopsy to validate your target is going to be much  
25  more difficult than an adult going to repeat

1 surgical resections. I mean, you can have targets  
2 which are not within the neural system but they are  
3 never going to hold up to the same level to the  
4 actual tumor cells. So, I think that is something  
5 that we have to keep in mind.

6 DR. FINE: Right, but the question that  
7 was posed by Victor's was, let's say, this receptor  
8 was a validated target in adults but doesn't exist  
9 in the pediatric tumor, what do you do with that?  
10 And, part of the issue gets to our experience with  
11 the RTIs, for instance, where we think we are so  
12 smart and that we know that this is the only target  
13 and, in fact, it may not be. One of the reasons  
14 that this drug X that targets this receptor is  
15 causing regression in xenografts may have something  
16 to do with its intended target but may have other  
17 effects, and do we want to give the pediatric  
18 population the ability to experience those other  
19 effects if we are not as smart as we think we are?

20 DR. GAJJAR: I think absolutely yes. The  
21 answer is a resounding yes. I think what we have  
22 learned from these therapies is that they are not  
23 as specific as they were designed. I think, you  
24 know, the metronomic dosing schedule with ordinary  
25 chemotherapy is now supposed to be anti-angiogenic

1 and we don't know the mechanisms. In diseases  
2 where the outcome is so poor I would not hold back  
3 a child from deriving a benefit because we were not  
4 smart enough to know the exact mechanism. I mean,  
5 the common end target may be the same but they  
6 could work through different receptors.

7 DR. FINE: That was the basis for my  
8 invoking the question.

9 DR. SANTANA: I tend to agree -- I am not  
10 going to call him Victor, I am going to call him  
11 Dr. Levin so we can differentiate between the two  
12 Victors. I agree with you. I think scientifically  
13 if the rationale doesn't exist in the pediatric  
14 counterpart you have no scientific basis to test  
15 the indication. So, if you are telling me that a  
16 glioma in adults expresses X receptor and somebody  
17 develops a biologic to treat that whether the  
18 Pediatric Rule should be invoked, and there is no  
19 scientific rationale to suggest that that receptor  
20 also exists in the gliomas why should we invoke the  
21 rule for a pediatric population when that specific  
22 target doesn't exist?

23 DR. PACKER: Except, you are going on the  
24 assumption that all of these targets have been  
25 looked at carefully in pediatrics --

1 DR. SANTANA: Yes.

2 DR. PACKER: -- given the heterogeneity of  
3 these tumors, the small sample size and the small  
4 numbers of patients, and you are going to be saying  
5 that we only will use biologic agents that have  
6 been already proven to have that target available  
7 in pediatrics, when you have just said yourself  
8 that you don't even know if it is the right target  
9 how it is being used.

10 DR. SANTANA: No, Roger. You are correct.  
11 I made the assumption that there was enough  
12 pediatric information to know that that receptor  
13 was not --

14 DR. PACKER: I think that is not a fair  
15 assumption in pediatric malignant or, for that  
16 matter, low grade glial tumor biology. Because I  
17 don't think that is going to be up and running --  
18 we don't have the cell lines for pediatric glio  
19 tumors; we don't have a lot of biologic data to  
20 hold that whole group of children away from these  
21 drugs if there is a good rationale -- and I would  
22 exclude the child under one possibly, but for  
23 anybody above that age, if there is a strong  
24 rationale to go ahead with it in adult trials I  
25 would suggest there should be a strong rationale to

1 go ahead with pediatric trials until you show me a  
2 series that has looked exhaustively at enough  
3 pediatric glial tumors to know that that pathway is  
4 not intact.

5 DR. LEVIN: I think we are arguing about  
6 things that we shouldn't be arguing about because  
7 the real issue is that we don't really have  
8 substantially better tools to deal with the target  
9 identification in adult tumors. And the goal  
10 really will have to be on a separate level to  
11 create systems for studying material from human  
12 tumors without having to rely completely on cell  
13 culture, which changes the genetics as well as the  
14 phenotype, and in animal models. So, we have a  
15 long way to go but there is nothing that will stop  
16 us, I believe, once we have the tools to use on any  
17 tumor from any age patient.

18 DR. SANTANA: I guess the analogy, Roger,  
19 is an analogy that was used earlier this morning  
20 with APL. If you have APL that does not carry the  
21 classic translocation involving the receptor would  
22 you subject that pediatric patient to treatment  
23 with retinoic acid?

24 DR. PACKER: It immediately goes back to  
25 Victor's comment. If we have a way to clearly know

1 that that is the case the answer is no. My problem  
2 is that the level of science that we have now  
3 cannot answer that question for pediatric brain  
4 tumors, specifically pediatric gliomas, and until  
5 we have that level of science I would suggest the  
6 rule should be invoked.

7 DR. SANTANA: Henry?

8 DR. FRIEDMAN: I agree with Roger totally,  
9 but Howard has made the point we are going to have  
10 to address. The practicality is that the Pediatric  
11 Rule will only help us in pediatric neuro-oncology  
12 for gliomas. We are going to get no help from the  
13 rule in virtually all the other tumors we see  
14 because there is no chance in hell that we are  
15 going to have an adult trial done in any of those  
16 other histologies, adult meningioblastoma for  
17 example. Therefore, the only way we will be able  
18 to get help from the application of the Pediatric  
19 Rule would be if a target is identified in another  
20 histology which then has a counterpart in pediatric  
21 neuro-oncology. There again, with everything you  
22 said, Howard, I agree, and Victor, with target  
23 identification we are going to have to be able to  
24 apply the rule in a non-histology specific fashion  
25 where we are going after a specific molecular

1 target and know that that target has at least some  
2 prevalence in pediatric tumors, otherwise it will  
3 never help us in anything but glioma.

4 DR. POMEROY: I would add definitely to  
5 that the danger of just going on histology alone is  
6 you will never answer the question. You will never  
7 know, unless you somehow study these tumors and  
8 develop a mechanism to understand the molecular  
9 basis we will never have a rational basis for  
10 treatment. We will just be shooting in the dark  
11 and using the same histology-based criteria that we  
12 have always had.

13 DR. SANTANA: Mike?

14 DR. LINK: If we developed a targeted  
15 specific therapy and we were mandating that a drug  
16 company applies it to a group of tumors where we  
17 have shown that the target doesn't exist, I mean,  
18 you would look like a dope, wouldn't you?

19 DR. FINE: Roger's point I think is the  
20 important point, which is again one of the reasons  
21 I brought this question up. The problem is we  
22 don't know so often in pediatric tumors and we are  
23 talking about how we are going to apply a rule this  
24 year. I mean, hopefully, five years from now or  
25 ten years from now we will know the answer, or

1 hopefully less than that we will know. But faced  
2 with drug X today that is in clinical trial for  
3 adults, the way you defend it is -- and, again,  
4 that is what this committee is here for, to try to  
5 help decide, but if you say that high grade  
6 glioblastoma in adult is the same as a glioblastoma  
7 child and that the EGFR is -- I am just saying if  
8 it is, if it is shown to be a validated target in  
9 the pathogenesis of adult glioblastoma then, by  
10 definition, it must be a validated target for  
11 pediatric GBM if you are saying that GBMs are the  
12 same across and so by extrapolation.

13           But ultimately you are right, once we have  
14 200 childhood GBMs for which that receptor is  
15 looked at, if it turns out it is not there, then I  
16 think everyone in this room would agree there would  
17 be no reason to use that drug. The question is,  
18 given the lack of that knowledge, what do we do  
19 when faced with drug X?

20           DR. MEYERS: But I think we are also  
21 making a presupposition that our target validation  
22 has been a hundred percent effective. Are you  
23 prepared to tell me that we know with this kind of  
24 pathway identification that these so-called  
25 targeted therapies work exclusively in the tumors

1 which have the target of interest? I mean, we have  
2 heard two examples, good examples. HER2 is  
3 expressed in a high percentage of breast cancer  
4 patients and only a small percentage of breast  
5 cancer patients respond to Trastuzumab. The ras  
6 inhibitors appear to work but probably not at all  
7 through that mechanism.

8 I think we are assuming a greater degree  
9 of knowledge and certainty than that to which we  
10 are entitled. I think I would say if a drug is  
11 appropriate to be tested in the gliomas of adults,  
12 it is appropriate that it be tested in pediatric  
13 gliomas. And it is not a question of targeting.  
14 We are just not there yet in terms of the certainty  
15 that the target is what we think it is and that the  
16 validation of the target exists in adults, much  
17 less in children.

18 DR. SANTANA: So, you are suggesting that  
19 part of the purpose of the conduct of the trial is  
20 to precisely not only test the therapy but test the  
21 validation of the therapy.

22 DR. LEVIN: But let's put ourselves in the  
23 real situation that we want to get access to drug  
24 for medulloblastoma. Okay? Now, we know that  
25 there are a variety of large groups of signaling

1 pathways. Say, ras, sarc, pkc are general  
2 pathways. Okay? And, some pharmaceutical company  
3 develops and inhibitor of one of the paths that  
4 works extraordinarily well in one of the  
5 adenocarcinomas but the people who study  
6 medulloblastoma know that if they can inhibit this  
7 pathway by a variety of different means it also has  
8 a positive effect on survival. Now the situation  
9 is would the FDA, under this rule, allow the  
10 pediatric specialty group to go to the  
11 pharmaceutical company and basically demand or  
12 expect to be able to get access to that drug? That  
13 is what the pediatric population needs, but the  
14 question is, is that a valid legal pursuit within  
15 the FDA? And, that is what I would suggest might  
16 be our future as we move forward with better  
17 signaling molecules. It will cover pathways. We  
18 will know whether those pathways are important or  
19 not. And, within some of those pathways we will be  
20 able to pick families of compounds that we think  
21 are more likely than not to be better for brain  
22 tumors than they would be for adenocarcinoma but we  
23 will have choices.

24 DR. MEYERS: I absolutely agree with you  
25 but I think that that is what we should be striving

1 to get to, but in order to go to a sponsor and  
2 compel them to extend a compound to an unrelated  
3 histology based on a pathway, I think they would  
4 say, well, let's first prove that it is effective  
5 in the primary indication and uniquely effective in  
6 those tumors which depend on that pathway which  
7 have modifications of that pathway. And, I don't  
8 think we have that quite yet.

9 DR. SANTANA: Larry?

10 DR. KUN: Yes, I think there are two  
11 different issues here. First of all, if there is  
12 an agent that shows clinical efficacy in a cohort  
13 of patients with adult malignant gliomas, for  
14 instance, then I would hate to see that precluded  
15 for any reason from trial in pediatric malignant  
16 gliomas. I don't think anybody around the table  
17 would really disagree with that.

18 I think the second point is a harder one  
19 to know. I mean, if an agent is specifically  
20 developed for a target unrelated to a tumor system,  
21 then at what point -- and this could in CNS or it  
22 could be in ALL, at what point do we go and say  
23 this drug should be available for pediatric trials?  
24 Given the fact that trials are the standard for  
25 therapy, so to speak, in pediatrics, you would like

1 to say that if there is a biological reason to  
2 study the drug and the preclinical model suggests  
3 that there is efficacy, then that should be  
4 available for the pediatric trial.

5 DR. SANTANA: Roger?

6 DR. PACKER: It is a leap of faith, but if  
7 this rule is going to be of help for  
8 medulloblastoma there is going to have to be some  
9 leap to say that if a drug has been found to be  
10 very effective in adult malignant gliomas, and we  
11 should live so long to find that drug --

12 [Laughter]

13 -- that it should be applicable to other  
14 pediatric brain tumors. I think you could make a  
15 cogent argument that they share enough pathways.  
16 We have not really been in that position that  
17 often. temazolomide is probably the best example  
18 of that and the drug company did not hold the drug  
19 back on that basis. I would ask the question a  
20 little bit differently because we are not going to  
21 be able to answer the first one, how do we roll  
22 this back to lower grade pediatric tumors, glial  
23 tumors? How do we roll it back when we don't know  
24 what those tumors have as far as biologic changes  
25 by and large, especially in pediatrics but I don't

1 think we know that much in adults either? Yet, if  
2 it is effective in adults with malignant gliomas  
3 and it is of low toxicity, can we roll it back to  
4 anaplastic and grade 2 tumors? My argument would  
5 be a strong yes, but I don't have a strong biologic  
6 basis to make that argument.

7           Similarly, if you are looking for reasons  
8 to suggest a drug should be utilized, it also could  
9 mechanism of action. If a drug is being developed  
10 that benefits control of leptomeningeal disease in  
11 another tumor type, then that drug, because it may  
12 have a major effect on tumor spread or  
13 dissemination or adhesion, should also be  
14 considered strongly for those kind of pediatric  
15 tumors where that is a major problem, such as  
16 medulloblastoma. So, I think it is more than just  
17 the genetic makeup of the tumor.

18           DR. SANTANA: Joe, did you have a comment?  
19 I thought earlier you wanted to say something.

20           DR. GOOTENBERG: Actually I would like the  
21 discussion to keep on going but at the end I want  
22 to ask a clarifying question. So, if there is more  
23 discussion to go, it should finish up.

24           DR. SANTANA: Dr. Burger, do you have any  
25 comments or want to join the discussion?

1 DR. BURGER: Not really. I can talk but I  
2 think this is a very complicated subject. If you  
3 have any specific questions about the pathology I  
4 would be glad to answer them.

5 DR. SANTANA: I just wanted to make sure  
6 that you did not feel we are leaving you out of  
7 this discussion.

8 DR. BURGER: No, I don't feel left out.

9 DR. SANTANA: Okay, good. Joe, do you  
10 want to go ahead and address your issue?

11 DR. GOOTENBERG: From the standpoint of  
12 biologics where I think a lot of this is going to  
13 be played out, I think that is the arena for the  
14 mechanism-specific indications that we might get, I  
15 think we need to clarify that what we are talking  
16 about here is the Pediatric Rule and that the  
17 Pediatric Rule is, number one, license application  
18 driven. It only comes in effect at that point.  
19 Number two is indication driven, and what we are  
20 talking about here is what we would consider the  
21 same indications so that under the law we could  
22 either mandate that studies are done or give some  
23 form of waiver.

24 Already our feeling is that in biologics  
25 in the future we are going to have indications that

1 combine the mechanism and the disease. This has  
2 already happened. For example, APL was mentioned.  
3 Retinoic acid is indicated for APL that has the  
4 translocation, not for any other APL. So, if that  
5 is found in pediatrics, no way would we begin it.

6 DR. HIRSCHFELD: Arsenic is a retinoic  
7 acid.

8 DR. GOOTENBERG: Okay, arsenic. For  
9 example, also you would look at monoclonal  
10 antibodies and look at Herceptin indication most  
11 likely -- I haven't looked at it recently -- is for  
12 antigen-positive breast cancers. So, we think that  
13 biologic indications in the future will be both  
14 mechanism and disease specific, and the question is  
15 whether we are going to focus on the mechanism and  
16 say that studies should be done or not.

17 DR. SANTANA: But I thought I heard Paul  
18 and Roger arguing the point that it should be both,  
19 that because of the limitation of patient numbers,  
20 in pediatrics in this particular scenario that you  
21 are proposing, which I think is the more likely one  
22 to be, that is, looking at both disease histology  
23 and a mechanism, we are not at the point yet that  
24 we have enough pediatric information for the  
25 mechanism validation that I think if a sponsor

1 comes to you with a biologic looking at both  
2 gliomas that express X, I think you should  
3 seriously consider allowing -- this is the argument  
4 that I hear from that side of the table -- that you  
5 should allow pediatric patients to have access to  
6 that drug without a full understanding whether  
7 mechanism X is operative.

8 DR. GOOTENBERG: That is not how the rule  
9 operates. We don't allow access to the drug. We  
10 either mandate that studies be done or we waive and  
11 say studies don't need to be done, and that is a  
12 big jump, a big gap there.

13 DR. KUN: But I think what we are saying  
14 is that that jump should be taken for the mechanism  
15 or for the histology.

16 DR. PACKER: If you don't you will never  
17 treat brain stem glioma on a study because we don't  
18 have tissue on brain stem gliomas, yet the vast  
19 majority of those patients will be dead within 9-18  
20 months of diagnosis. You have to make that jump if  
21 you are going to affect the field. If the mandate  
22 is the only way to get the drug there, then I would  
23 suggest you use the mandate.

24 DR. SANTANA: Donna?

25 DR. PRZEPIORKA: Just a request for a

1 clarification from Howard Fine, please, because  
2 what it sounds like from that side of the room is  
3 that a glioma is a glioma is a glioma --

4 [Laughter]

5 -- similar to the sarcoma story and adults  
6 and pediatric patients should be treated the same  
7 way. Yet, I recall from your slides that adults  
8 and pediatric patients are treated differently.  
9 So, my question is are they treated differently  
10 because the tumors are different or are they  
11 treated differently because of tradition?

12 DR. FINE: Again, as I tried to explain,  
13 high grade gliomas are not treated differently.  
14 Low grade gliomas are treated differently. Because  
15 a glioma is not a glioma is not a glioma, in our  
16 ignorance we treat a glioma as a glioma as a glioma  
17 within the adult population. Hence, we can  
18 extrapolate and say since we do that with adults,  
19 we can do that with children too because it may  
20 very well be that the real subtypes of tumors that  
21 we classify as gliomas may not go across age groups  
22 but will go across genetics. But we are not there.  
23 So, given our state of ignorance, the question is  
24 should we then just treat them all the same? If  
25 that is true, then we invoke the Pediatric Rule.

1 DR. GROSSMAN: I think the other  
2 difference is if radiation therapy were as  
3 neurotoxic to the adults as it were to the  
4 children, we actually would treat everybody the  
5 same.

6 DR. FINE: But, Skip, do you really think  
7 that you can get a 70-80 percent response rate with  
8 carboplatinum with your average low grade  
9 astrocytoma in adults?

10 DR. GROSSMAN: No. There are differences  
11 in terms of survival between adults and kids in  
12 sarcomas and other diseases that we talk about too.  
13 I am not saying that that makes them absolutely  
14 identical, but I think if we had severe  
15 neurotoxicity from brain irradiation in adults, we  
16 would be pushing a lot more chemotherapy in the low  
17 grade astrocytomas.

18 DR. FINE: Right, but I think it is still  
19 an important point, especially the low grade, that  
20 there must be something different about it, because  
21 it is not that we can't get to those doses with  
22 carboplatinum into a 25-year old but we don't see  
23 the kinds of responses that Roger and others have  
24 reported.

25 DR. LEVIN: One, we do see a lot of

1 irradiation toxicity so we do have a reason to push  
2 chemo. Two, all low grade gliomas in childhood are  
3 not infiltrated tumors. Most of the low grade  
4 tumors in adults are infiltrated tumors. The third  
5 thing is that I believe that the conversion of low  
6 grade infiltrate of gliomas of childhood to adults  
7 approaches 50-70 percent depending on year. In the  
8 Gillis article it is basically 70 percent at 5  
9 years because they are talking about  
10 progression-free survival of astrocytoma being 0.7.  
11 So, that being the case, there must be a conversion  
12 rate of 30 percent in 5 years just from the Gillis  
13 paper.

14 DR. KUN: Just because they fail doesn't  
15 mean they convert.

16 DR. LEVIN: Yes, but my guess is they do  
17 convert.

18 DR. KUN: Well, a percentage of them do  
19 but it doesn't seem to be that high.

20 DR. LEVIN: For infiltrative low grade  
21 gliomas.

22 DR. PACKER: If you look pathology  
23 studies, I don't think that is correct but low  
24 grade infiltrating tumors in pediatrics are not  
25 benign processes whether we call them benign

1 tumors. Again, we get caught up in how we label  
2 these things but those are tumors that require  
3 treatment and they are tumors that often are not  
4 treatable with radiation because of the extent of  
5 the disease, and we need alternatives without  
6 biologic data to support what we are going to  
7 utilize, and we are stuck with empiric approaches.

8 DR. ELIAS: Yes, I just wanted to get back  
9 to the issue of the burden of proof. If one uses  
10 histology, I think the burden of proof is in a  
11 sense invoking the Pediatric Rule because we have  
12 the natural history of the tumor, the biologic  
13 behavior, the years of experience with looking at  
14 histology. I think when we are talking about  
15 pathways we have a different burden, one of which  
16 is that we know that very few of our pathways are  
17 clear, single, straight line pathways. They all  
18 have multiple effects. Many of the drugs that  
19 target against one thing clearly have effects on  
20 other targets.

21 So, in a sense if we had the issue of  
22 medulloblastoma and let's say it shared a pathway  
23 with lung cancer, the issue is what would it allow  
24 us to invoke? Clearly, not just the fact that the  
25 pathway was shared when we clearly have to be able

1 to demonstrate in a certain sense not just that it  
2 is present but that it is fundamentally important  
3 in both tumors, do you need animal models? Do you  
4 need clinical data? What level of proof do you  
5 need to show that that pathways is, in fact,  
6 important in medulloblastoma in order to invoke the  
7 Pediatric Rule?

8 DR. HIRSCHFELD: The answer isn't in yet  
9 because that is why we are having these discussions  
10 to try to evolve what approach to take. Clearly,  
11 the modalities in terms of burden of evidence you  
12 discussed are all the relevant modalities. It is,  
13 in a way, a variation on the figure that we are  
14 often asked by industry sponsors, what percent  
15 response rate do we need in order to get approval?  
16 And, we don't know. We never fixed that number.

17 But I think that when there is some level  
18 of consensus in the scientific community that this  
19 is the accepted mechanism, then I think it would  
20 become relatively apparent. We need to have a  
21 formal ruling on it.

22 DR. PAZDUR: Basically it is concurrence  
23 of the medical community. So, the issue here is  
24 that it is a widely held scientific medical belief.  
25 The Pediatric Rule can't be invoked for hypothesis

1 generating, basically, it is to take something that  
2 is already established and apply basically a  
3 diagnosis or a principle.

4 Questions to the Committee

5 DR. SANTANA: I am going to go ahead and  
6 try to tackle the questions so we can finish on  
7 time.

8 I would suggest that for question A, what  
9 general principles could be used to relate CNS  
10 malignancies in adults to CNS malignancies in  
11 children, that we follow the model that we proposed  
12 this morning for sarcomas because I think there are  
13 more similarities in adult and pediatric brain  
14 tumors than there are with the prior discussion  
15 earlier this afternoon. So, I would invoke that we  
16 consider histology as a primary -- not the only but  
17 as a primary determinant and, in addition, special  
18 considerations to molecular characterization and,  
19 in addition, something that we have kind of not  
20 completely discussed but I want to throw in, with  
21 some special attention to issues of safety,  
22 particularly with neurocognitive. I know that that  
23 is not how the indications are done but ultimately  
24 the labeling has to address that.

25 So, I think in this particular group of

1 diseases, the brain tumors, I would propose that  
2 histology and molecular characterization be the  
3 guiding principles but with some special attention  
4 to issues of safety as it relates to labeling, and  
5 if they don't exist, you know, the sponsors have to  
6 say they don't exist. But we should encourage them  
7 to look for those when these trials are done so  
8 that the labels accurately reflect that particular  
9 segment of this population. Larry?

10 DR. KUN: But am I incorrect? Isn't the  
11 labeling a secondary event?

12 DR. SANTANA: Yes.

13 DR. KUN: What you are trying to do here  
14 is establish the precedent that the drug would be  
15 available for study --

16 DR. SANTANA: Right.

17 DR. KUN: -- and you won't know the impact  
18 upon subsequent neurocognitive function, except to  
19 be confident that it is a part of the study where  
20 appropriate.

21 DR. SANTANA: Right, I just wanted to make  
22 people sensitive to that issue, not that it is an  
23 issue of the primary indication, Larry.

24 DR. PACKER: But wouldn't that be more of  
25 an issue of clinical trial development, of how you

1 do the trials in pediatrics, rather than getting  
2 the drug to pediatrics? Then, you said you had  
3 another meeting coming up on clinical trials. As  
4 you move it to pediatrics there have to be some  
5 specific safeguards brought in.

6           The one thing I did want to add, and I  
7 don't know if it is covered by talking about  
8 pathways, is again some statement if also the drug  
9 is aimed at a specific pattern of disease spread  
10 that would be particularly useful in pediatrics,  
11 i.e., leptomenigeal spread. That would be another  
12 indication potentially if you were developing an  
13 intrathecal drug for carcinomatous meningitis. If  
14 that drug showed significant efficacy, to try to  
15 make that drug available for pediatric tumors that  
16 have leptomenigeal spread. I don't know how to  
17 put that in wording but I wonder if that shouldn't  
18 be also in the back of people's minds as they put  
19 this together.

20           DR. SANTANA: Richard or Steve, did you  
21 get that message? Good.

22           DR. HIRSCHFELD: Right, I would fold that  
23 into what we call the natural history  
24 characterization.

25           DR. POMEROY: I would only add that as far

1 as the lack of knowledge in pediatric brain tumors,  
2 a number of us feel passionately that we want to  
3 fill in that gap and build that up as part of the  
4 criteria that we ultimately will use in extending  
5 studies to the children.

6 DR. SANTANA: Any further advice regarding  
7 issue A to the agency?

8 [No response]

9 For question B, which of the following  
10 adult diseases has a pediatric counterpart and what  
11 is the basis? I think, if the committee will allow  
12 me, I would venture to say that if not all, for  
13 many of these I think there are a similar disease  
14 correlates and I don't think we need to discuss  
15 those further.

16 Then the question that I always have  
17 trouble with, which is the issue of the exception  
18 examples that keeps coming back --

19 DR. HIRSCHFELD: This is the last time you  
20 will see this question, and specifically that is  
21 why we invited Dr. Perlman to see if there were any  
22 ways -- again, it is just an attempt to be  
23 comprehensive and complete.

24 DR. PERLMAN: Your question with regard to  
25 germ cell tumors and their different

1 classifications, regarding question C, I don't see  
2 any risk or any problem with a different  
3 classification of a germ cell tumor as anything  
4 else. With regard to whether or not there is a  
5 pediatric counterpart of germ cell tumors, I think  
6 regardless of the CNS or gonadal origin, and if you  
7 are talking about malignant germ cell tumors, there  
8 are two biologically separate categories, those  
9 that arise in prepubertal or, actually usually  
10 infants, and those that arise in postpubertal  
11 patients. Biologically, if you are confining  
12 yourself to those two categories, either of those  
13 two categories are biologically equivalent and,  
14 therefore, with regard to the CNS germ cell tumors,  
15 the number of infantile malignant CNS germ cell  
16 tumors are so extraordinarily rare I am not sure it  
17 needs to be addressed with this question.

18 DR. SANTANA: Any other comments regarding  
19 that? If not, I am going to try to finish on time  
20 and I will invite Dr. Meyers and Dr. Levin in  
21 succession to give us some summary comments.  
22 Peter, we are going to have some summary comments  
23 by Dr. Meyers and Levin. You are welcome to stay  
24 on board if you wish.

25 DR. BURGER: Okay, thanks.

1 DR. SANTANA: Thank you, Peter.

2 Summary Comments

3 DR. MEYERS: Thank you very much. I am  
4 going to start just be reminding all of us of the  
5 reason that we came here today. The purpose of the  
6 Pediatric Rule is to ensure that we make available  
7 to children, and specifically today to children  
8 with cancer, the newest drugs in a rapid and timely  
9 fashion so that we can learn their value in the  
10 treatment of children.

11 The FDAMA initiative which has been very  
12 successful and very effective in bringing a number  
13 of drugs to pediatric trial is not relevant. It  
14 doesn't do that early in the development of drugs,  
15 and what we are trying to do is get drugs in early  
16 development into appropriate pediatric trials.

17 So, I think that the meeting that you are  
18 going to have, which will follow this meeting, to  
19 address clinical trial design is really crucial in  
20 this whole process because the point I was trying  
21 to make earlier and the point that David Poplack  
22 referred to in the development of ATRA and other  
23 drugs for APLM is that for a lot of these drugs we  
24 need to find some way to get out of the paradigm  
25 that you have to complete the adult trials before

1 we can initiate trials in children.

2 I think this is especially important in  
3 looking at biological compounds, and in biological  
4 compounds it is going to be unusual that we are  
5 going to seek to achieve a maximum tolerated dose  
6 in the same way that we have done for traditional  
7 cytotoxic chemotherapy. We are going to be looking  
8 for evidence of biologic activity which will often  
9 be seen long before we see severe toxicity, similar  
10 to that which we are all accustomed to in our  
11 patients with cytotoxic chemotherapy. For that  
12 reason, I think it is legitimate to challenge the  
13 classic paradigm that one cannot initiate Phase I  
14 trials in pediatrics until adult Phase I trials are  
15 completed or nearly completed.

16 Someone this morning said we shouldn't use  
17 drugs until we have an understanding of how they  
18 work, like vincristine. I disagree with that  
19 statement. I think there is quite a little room  
20 for empiricism in oncology and, as much as I am an  
21 advocate of learning about pathways and their role  
22 in malignancies and identifying targets to address  
23 those pathways, I think we are far from being smart  
24 enough to say with certainty that a given pathway  
25 is central to a disease, and our targets are not

1 always we think they are.

2           This morning we led off with sarcomas. I  
3 think that was a wise decision because it allowed  
4 us to come to some consensus early on before we  
5 tackled the more contentious histologies that were  
6 under discussion today. I would suggest that we  
7 came to a fairly unanimous conclusion that the  
8 sarcomas need to be addressed in the same way in  
9 children and adults, and that there really is no  
10 reason to use an artificial divide between  
11 pediatrics and internal medicine when it comes to  
12 the sarcomas.

13           I think when we started to look at the  
14 neuroendocrine tumors, specifically the  
15 neuroblastoma versus the small cell lung cancer  
16 question, we saw some extremely intriguing data  
17 and, to me, very educational data but I am not sure  
18 that we reached a consensus that any drug which was  
19 automatically valuable in small cell lung cancer  
20 should invoke the Pediatric Rule for neuroblastoma,  
21 and I think we came to a similar consensus in brain  
22 tumors.

23           I think the other discussion we initiated  
24 here today and we did not complete was what, in  
25 fact, will be the basis for the indication

1 invocation, and will it be histology alone? Will  
2 it be histology and molecular pathology? Will it  
3 be some form of targeted pathway? I think the  
4 group continues to believe that histology is  
5 certainly still the first indication but that  
6 increasingly we will be looking at molecular  
7 pathology and pathway identification to invoke the  
8 rule.

9 I think the final point that I would make  
10 that I don't think we thought about completely  
11 today is that I think our biggest problem is  
12 ultimately going to be one of prioritization.  
13 Malcolm reminds us appropriately that our ability  
14 to carry out trials in pediatrics is ultimately  
15 limited by the willingness of patients to  
16 participate and the number of patients who are  
17 appropriate to participate, and he has told you  
18 quite accurately if we could accomplish trials very  
19 four to five years I would be pleased. I think it  
20 has been a little less than every four to five  
21 years in some of our sarcomas, but we are talking  
22 here about earlier trials, smaller trials, trials  
23 in patients who have had progressive disease or who  
24 have presented with high risk disease and even in  
25 that population we are dealing with very small

1 numbers. I think it is our responsibility, from  
2 the academic community, to make sure that we  
3 prioritize the choice of drugs which we wish to  
4 pursue, whether the rule is invoked or not, to  
5 ensure that we are bringing to the children with  
6 malignancies the best that we have to offer.

7 I think that prioritization will be based  
8 in part upon availability, in part upon some of the  
9 initiatives that were started yesterday at NCI to  
10 develop some preclinical screening tools, and in  
11 part upon risk/benefit ratios which will be  
12 identified at some point in the development of the  
13 drugs in adults or in preclinical testing.

14 So, I would say that I have found today's  
15 discussion immensely helpful to me and I am very  
16 grateful to have been allowed to participate.

17 Thank you.

18 DR. LEVIN: This is my first participation  
19 in some kind of an activity like this so I didn't  
20 really know how to prepare my comments, but since I  
21 am not a medical oncologist or pediatric oncologist  
22 I focused on brain tumors, which I have been doing  
23 for the last 28 years.

24 I will focus my comments primarily on  
25 brain tumors but will generalize a little. There

1 is no question that at least within brain tumors  
2 and outside of brain tumors there is some  
3 inexactitude and difficulty in making the correct  
4 diagnosis and some insecurity about that. Within  
5 adults and children there are going to be defined  
6 differences both at a molecular and genetic level,  
7 and there are going to be time-dependent  
8 differences probably in terms of biologic behavior  
9 that we incompletely understand now based on the  
10 molecular and genetic understanding we have today,  
11 but maybe tomorrow we will understand more fully  
12 what those patterns are, why biologic changes in  
13 the behavior of the tumor and survival occur. But  
14 today we can accept the fact that we don't know  
15 everything.

16           Given the similarities that were so nicely  
17 put forth by Henry Friedman, we can feel confident  
18 that within the sphere of gliomas, nerve sheath  
19 tumors, meningeal tumors, germ cell tumors, primary  
20 CNS lymphomas and sellar tumors that we can go  
21 forth in concert with pediatrics.

22           I think the issue from my perspective is  
23 for each individual tumor what is the way to move  
24 forward the fastest to get the treatment to the  
25 child? Clearly, the fastest way to get a treatment

1 for neuroblastoma to children is to do it in adults  
2 where you can accrue patients for Phase II studies  
3 in three months. It goes forward with the  
4 anaplastic tumors as well.

5           So, I think the issue probably shouldn't  
6 be so much age as it is getting the study done and  
7 validation that against this disease this is a  
8 valid treatment. Then maybe lessening the  
9 requirements in pediatrics to just proving that it  
10 is safe and that the PK supports the dose that is  
11 being used, and to focus less on the initial  
12 efficacy study trying to rediscover the wheel, but  
13 trying to get the therapy into the patients as fast  
14 as possible.

15           When you deal with primitive  
16 neuroendocrine tumors the world is topsy-turvy  
17 because there is no adult correlated. There, I  
18 think it is going to have to be individual  
19 cleverness, really seriously looking at signaling  
20 pathways. People say they would like to do  
21 empiricism, but empiricism has gotten us very  
22 little distance in the treatment of glial tumors  
23 and in the treatment of medulloblastoma. The  
24 number of different types of treatments that have  
25 really come forward is very small. Basically, they

1 are the same that have been used in general for the  
2 past decade or longer. So, that really does not  
3 hold for primary brain tumors. For primary brain  
4 tumors we really are going to have to create more  
5 knowledge and attract either the development of new  
6 drugs or to get the companies and the inventors of  
7 these drugs to allow us to get access to them  
8 sooner so we can study them in animals, so we can  
9 make a stronger justification for using them in  
10 people more quickly.

11 I really don't think that there is an easy  
12 way around the solution for finding a therapy for  
13 uncommon tumors. I think you have to do it on an  
14 individual basis and you have to provide sufficient  
15 evidence that can justify its use in that disease.  
16 I think random empiricism in this day and age is  
17 probably not cost effective. There are going to be  
18 too many options coming forward with respect to  
19 drugs. It is very easy to make drugs today, much,  
20 much more easy than it was years and years ago.

21 The biggest problem today is the targets.  
22 So, in that process the companies are going to come  
23 forward with large numbers of inhibitors of  
24 specific targets, and I think the pediatric field  
25 could be overrun by the empiricism and trying to

1 combine them. So, I think trying to, at the same  
2 time, create a knowledge base will turn out to be  
3 the most time effective way of getting treatment to  
4 the clinic fastest.

5 I think that that basically summarizes my  
6 thoughts, at least from a brain tumor perspective.  
7 I am having a hard time understanding how invoking  
8 this would really help at this stage.

9 DR. SANTANA: I want to thank Victor and  
10 Paul for their summary statements. I want to ask  
11 if Steve or Richard have any concluding remarks  
12 before I make a final statement.

13 DR. HIRSCHFELD: I would like to thank  
14 all the members of the committee and the speakers  
15 who put in the extra effort. I would like to thank  
16 the members of our Division, particularly the  
17 Director, Dr. Pazdur, and my pediatric oncology  
18 colleagues, Drs. Al Shapiro and Ramsey Dagger.  
19 And, I would like to thank Victor Santana for once  
20 again leading an outstanding panel discussion.

21 DR. SANTANA: Thank you. Susan wants to  
22 make a final comment and Jerry wants to make a  
23 final comment, and I am going to take the  
24 chairman's prerogative and allow them to do that.  
25 Susan, please?

1           DR. WEINER: Thank you. Just one final  
2 question I think for Dr. Pazdur and Dr. Hirschfeld,  
3 there has been a lot of healthy and exciting  
4 disagreement in this room today, including  
5 disagreement from the final summary statements  
6 about whether, for example, the adult paradigm  
7 should continue or not continue in pediatrics, or  
8 whether or not we should forego empiricism for  
9 targeted therapies or vice versa. I guess because  
10 of that disagreement and because of the anxiety  
11 that inevitably incurs in patients and families, I  
12 would like to hear something about how those kinds  
13 of disagreements in the community will be resolved,  
14 and what the interface will be with the cooperative  
15 groups and the community in general. I think that  
16 that would really put us in a position of going out  
17 in the world and saying we are certain that this is  
18 going to be a sound and rational procedure.

19           DR. PAZDUR: I think the answer to your  
20 question, Susan, is time. One of the reasons I  
21 think you have found a lot of disagreement here is  
22 that the scientific underpinnings of most of the  
23 questions that we are trying to answer are still in  
24 their relative infancy. Everybody would like to  
25 have targeted therapies. It makes sense. However,

1 oncology has been one discipline of empiricism  
2 which I think all of us we like to see come to an  
3 end and have a more rational development of drugs.  
4 But I think that is going to take time and the  
5 disagreement that I think you saw here among many  
6 of the people represents an absence of data rather  
7 than an abundance of data. I think as we develop  
8 more targeted therapies and look closer into this  
9 field, hopefully, we will have a greater database  
10 to come to some consensus.

11 DR. HIRSCHFELD: Could I just add that  
12 this will be an ongoing discussion. Today was  
13 perhaps the beginning but it certainly doesn't  
14 represent the end of this dialogue.

15 DR. WEINER: But there will be some formal  
16 structure, some entity that will continue to look  
17 at the questions that plague pediatric oncology  
18 about access to drugs and about what is to be  
19 tested, given the bulging pipeline?

20 DR. PAZDUR: Yes, this subcommittee will  
21 continue. Obviously, this is not just three  
22 meetings and then we are going to call it quits  
23 here. So, yes, this is an ongoing commitment that  
24 the Division has to pediatrics. In addition,  
25 obviously when we do have pediatric questions, as

1 with adult questions about malignancies, we bring  
2 in pediatricians that are on this committee to  
3 answer questions that we have. But, yes, this is  
4 an ongoing commitment that we have.

5 DR. SANTANA: Yes, and I think a follow-up  
6 to that is I hope that this dialogue is not two-way  
7 but it includes the cooperative groups very  
8 seriously in this discussion, CTAP. Sponsors,  
9 obviously, are an important point. So, I was glad  
10 to see that a number of sponsors showed up today  
11 and that Malcolm was here and that other  
12 representatives in other roles of leadership in the  
13 cooperative group were also here because I think it  
14 is not only a dialogue between the FDA and the  
15 sponsors; it is a dialogue I think, Susan, that  
16 involves other people and I think, either through  
17 this structure of additional structures, we need to  
18 keep that going. Jerry?

19 DR. FINKLESTEIN: Sixteen months ago --  
20 not long ago -- I had the opportunity to co-chair a  
21 meeting held at the American Academy of Pediatrics  
22 downtown office in Washington. There were seven  
23 groups attending, many of whom are here today. The  
24 FDA was there; the public was there; Susan was  
25 there; leaders in pediatric oncology were there;

1 members of PhARMA were there; pharmacologists were  
2 there. NCI was represented by a number of people,  
3 including Malcolm. Leaders of the American Academy  
4 of Pediatrics were there, and for one of the  
5 sessions there were staff represented from people  
6 from Congress.

7           The goal of the meeting was to see what  
8 could be done by having all these groups sit around  
9 the table to look at drugs and therapies for  
10 children with cancer and bring them earlier to the  
11 child who is suffering this very devastating  
12 disease. Now, this is the third meeting of an  
13 FDA-created committee. I have to tell you that at  
14 that meeting the FDA went into a separate little  
15 meeting -- I remember it -- behind me, Richard,  
16 Steven, Dianne Murphy and Mac Lumpkin went into a  
17 room, closed the door as we were all struggling  
18 with this; came out. Mack grabbed the blackboard  
19 and said we can help. Obviously, they looked at  
20 their mandate and they realized that they could  
21 come to the table and accept the challenge.

22           Now, I am probably the senior pediatric  
23 oncologist in this room, and for decades, in my  
24 mind, it was always "we" and "they." When they  
25 grabbed that blackboard I realized it was "we" and

1 "we" because there is no question in my mind that  
2 they have stepped to the plate.

3 Susan, there is no question in my mind  
4 that they are going to continue and I would like to  
5 congratulate Richard -- incidentally, Richard is a  
6 medical oncologist who thinks like a pediatrician  
7 so I have to doubly congratulate Richard and I  
8 certainly congratulate Steven for grabbing the  
9 balls and keeping it going, and I look forward to  
10 further deliberations of this group and I thank you  
11 on behalf of my patients.

12 DR. SANTANA: Thank you. I think we are  
13 adjourned and I think we have done our task that  
14 was assigned. Have a good day.

15 [Whereupon, at 3:40 p.m., the proceedings  
16 were recessed.]

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