

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 lot longer than the adult? I think that is
2 something to consider as far as the Pediatric Rule.

3 Then, finally, the one thing I haven't
4 talked about and a major issue as far as
5 neuro-oncology in the population are brain stem
6 gliomas. These tumors appear to have unique
7 radiographic and clinical correlates. Although
8 pathologically these tumors appear to be similar to
9 supratentorial gliomas, they do appear to behave
10 differently. Should they be treated differently?
11 I actually don't have a firm answer about that and
12 I think that is worth some discussion. So, thanks.

13 DR. SANTANA: Thank you, Howard. Dr.
14 Burger, are you still on the phone? I guess not.

15 DR. FINE: That is usually what happens
16 when I talk.

17 [Laughter]

18 Discussion

19 DR. SANTANA: I just wanted to see if he
20 was still connected to see if he had any comments
21 on the two presentations. I want to get back to
22 one of the last issues that Howard challenged us to
23 try to answer to start the discussion because it
24 came up earlier this morning too. And I would like
25 to hear some feedback from various members of the

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 pathway 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 APML 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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