

1 | dose-response curve we're looking at.

2 | But there are statistical methodologies that
3 | have recently been put forth -- specifically, to continue
4 | reassessment method -- that might make more efficient use
5 | of patient resources that we have available if we could
6 | somehow break out of this mold that we've been comfortable
7 | of 3 and 6. I realize that there are some arguments one
8 | way or the other. But I think that maybe at least the
9 | people in the position to enforce the designs that we're
10 | able to use should take a step backwards and consider that
11 | situation.

12 | DR. SANTANA: Richard, I saw you shake your
13 | head over there.

14 | DR. PAZDUR: We're not real big fans on
15 | continual reassessment method in the division. We've had a
16 | lot of problems with it.

17 | But I guess several questions. Is this whole
18 | concept of maximum tolerated dose the right concept? It's
19 | one if you take a look at other therapeutic areas which
20 | would never be accepted if you were developing a
21 | cardiovascular disease and we've kind of given ourself
22 | carte blanche to use maximally tolerated doses to inflict a
23 | great deal of toxicity on people with the rationale only,
24 | well, these poor people are dying anyway, so maybe this
25 | will work. This would never be an acceptable approach.

1 There is no attempt ever in oncology to do any
2 dose-ranging studies, and I think that this is particularly
3 important in pediatrics where you do have long-term
4 toxicities that potentially could be ameliorated or changed
5 if you went down in a dose perhaps. Is there ever any
6 attempt, when you get a maximum tolerated dose, to find a
7 successful drug in pediatric oncology, to ask yourself a
8 question, are we using too high of a dose? Can we step
9 back down? And that's difficult to do. It's difficult to
10 do in adults, and it's one of these fundamental questions.

11 We as a discipline of medical oncology have
12 bought this concept of more is better, more is better, more
13 is better, and I think it's reached its zenith with bone
14 marrow transplantation. But it doesn't necessarily have a
15 lot of proof in this concept of optimal dose versus maximum
16 tolerated dose, and especially in pediatrics. Perhaps
17 you're taking some of our wrong examples and applying them
18 to pediatrics.

19 Comment?

20 DR. BALIS: There are very few trials that look
21 specifically at dose intensity in a way that it can be
22 evaluated at a dose level. There are lots of studies that
23 do more dose-intensive therapy, but they add new drugs to
24 make it dose-intensive.

25 One of the few is a randomized study that was

1 done I think back in the 1970s in a very small population
2 of patients where they looked at full-dose versus half-dose
3 maintenance therapy and that maintenance therapy was 6-MP,
4 methotrexate and cytoxan orally, and with 20 some patients
5 per arm, there was a significant difference in favor of the
6 full-dose therapy.

7 But there's not a whole lot of other data that
8 you can look at, and we're well beyond that degree of dose
9 intensity at this point, so I don't think that you can
10 apply to what we currently do.

11 The big problem, when you look at it in a
12 global sense, the reason that we don't use therapeutic
13 endpoints is that most of the drugs we've been studying
14 have been selected by random screening. We don't even know
15 what the mechanism of action is of many of them when they
16 go into the clinic. It was years before we learned how
17 doxorubicin worked, many years after we had it. So, we
18 can't look at a target in that sense.

19 There aren't really any good cellular assays
20 that can be done.

21 So, we're left with response or survival as
22 therapeutic endpoints. Response takes months to measure.
23 Survival takes years. So, we're stuck with our only effect
24 that we can measure acutely as being toxicity. So, it's by
25 default that we do it not by the fact that we want to.

1 DR. PAZDUR: One of the other paradigms you've
2 taken from adult medical oncology, you take our success
3 stories in a sense of drugs that are actively being
4 developed and examining those drugs in pediatrics. Do you
5 ever take a look at drugs that have been abandoned
6 basically? Because obviously there are differences in
7 tumor types, there are differences in toxicity and dose
8 between children and adults. Could there be some drugs
9 that we're discarding in adult medical oncology that may be
10 actually useful in pediatrics?

11 DR. BALIS: I think that would probably be a
12 drug company's worst nightmare.

13 (Laughter.)

14 DR. BALIS: To find a drug that works in
15 Ewing's sarcoma and no other disease and then try to tell
16 the public they weren't going to make it commercially
17 available.

18 DR. PAZDUR: I'm just being a devil's advocate
19 here.

20 DR. BALIS: For practical reasons we don't do
21 that just because it would become a major issue in terms of
22 getting it on the market when it's not going to ever be
23 profitable.

24 DR. FRIEDMAN: It's hard enough when they make
25 money with the adults. When they don't make money, it's

1 just not going to happen.

2 DR. PAZDUR: Last question. Any toxicities
3 that are unique to the pediatric population with the common
4 drugs that we use that we don't see in adults at all but
5 are specific to pediatrics?

6 DR. BALIS: I would agree with Victor's comment
7 that the spectrum, at least with cytotoxic drugs, is the
8 same. It may be that severity and the long-term effects
9 are different. But maybe the long-term effects are
10 different because we have patients that survive. We might
11 see the same thing in adults if they lived long enough.

12 DR. SANTANA: Donna, I think you're next.

13 DR. PRZEPIORKA: You showed the difference
14 within the pediatric group between the MTDs for heavily
15 pretreated and not so heavily pretreated patients, and you
16 also alluded to the fact that disposition of drugs changes
17 across age within the pediatric age group. Is there enough
18 change to suggest that phase I studies may need to be done
19 in separate pediatric age groups within the ages themselves
20 or to have some design that says very young patients must
21 be entered at every level in order to really get the MTD
22 down straight? Or is normalizing dose by body surface area
23 going to be enough to correct for that?

24 DR. BALIS: Well, for many drugs, when we've
25 looked at them across the age group where cancers occur --

1 and we rarely get children under 1 in phase I trials for
2 many reasons, some of which is that when they recur,
3 they're obviously past that age. The other problem is that
4 a 1-year-old who's been heavily pretreated for cancer,
5 particularly in terms of metabolic enzyme activity, is not
6 going to be at all reflective of what a normal 1-year-old
7 is going to be.

8 The way we've approached that is to try to make
9 sure that we had a broad spectrum in terms of age at the
10 MTD and not try to do it at each dose level because accrual
11 of these studies is difficult enough, and if you've
12 restricted it to requiring younger age patients before you
13 escalate the dose, I think it would become a much more
14 arduous and longer process to complete.

15 So, for example, when we reach an MTD, we try
16 to make sure that we have at least 3 to 6 patients under 12
17 and over 12. Even that probably isn't sufficient based on
18 what we know about pharmacokinetics to divide the groups
19 up.

20 It's not oftentimes until we get into phase III
21 that we refine that, and a good example of that is
22 vincristine, which had been in practice for years before we
23 determined that basing dose on body surface area,
24 particularly in young children, was probably too toxic. We
25 did pharmacokinetic studies to discover that and then alter

1 the way we gave the drug. But that certainly I think was
2 probably beyond what we could do in phase I testing with
3 the numbers of patients that we put onto these trials.

4 There's so much variability in pharmacokinetics
5 within even the same age group of patients, that detecting
6 differences among age groups requires too large a number of
7 patients to do it in a phase I study.

8 DR. SANTANA: One last question from the
9 members here, and then I think there's an audience member
10 who wants to make a comment. Malcolm?

11 DR. SMITH: I just wanted to respond to a
12 couple of Richard Pazdur's comments. One, how difficult it
13 is to determine the optimal dose for any agent because it
14 really becomes a phase III question. Is this dose or one-
15 and-a-half times this dose better? That's a comparison and
16 you really get into the phase III setting.

17 The way we've looked at that in the recent past
18 has been primarily if we give more, will it be better, and
19 looking at that in a systematic fashion. The recent
20 Ewing's sarcoma trial randomized patients to standard but
21 intensive therapy to very intensive therapy, and those
22 results will be maturing in the next year. But it's very
23 difficult to address those questions because they do become
24 phase III -- they're important questions. It's just that
25 they're very hard to address.

1 We have in Wilms' tumor the example of backing
2 away on therapy, not in intensity per se, but on duration
3 of therapy, and then realizing that long duration wasn't
4 necessary. So, those kind of questions are being asked.
5 In both those cases, they were phase III questions.

6 In terms of missed drugs, I'd like to second
7 something that Victor said before. I think a number of us
8 look at small cell lung cancer. When we see an adult-trial
9 drug coming through and we see the trials, we look there
10 and we get our clues there from whether this drug might be
11 active for neuroblastoma or for some of the other chemo-
12 responsive tumors.

13 A final point concerning the therapeutic
14 targets and the adult tumors and pediatric tumors are
15 distinctive molecular pathways to development. We may be
16 lucky, though. The other way of looking at it is that the
17 survival pathways that are activated or the apoptosis
18 pathways that are inhibited may be shared by fractions of
19 adult tumors and pediatric tumors. So, the real key
20 targets in survival pathways or real key targets in
21 apoptosis pathways may be the same in some of the adult
22 cancers and the pediatric cancers. We can take those drugs
23 and apply them to specific pediatric cancers.

24 DR. SANTANA: I would agree with that. I think
25 we're so focused on the early events, that it may be the

1 ultimate event that leads to death that's very common. As
2 long as you get there, it doesn't matter how you get there.

3 I think there was a member of the audience who
4 wanted to make a comment. If you could go to the
5 microphone and identify yourself please.

6 DR. UNGERLEIDER: I'm Rick Ungerleider from the
7 National Cancer Institute.

8 It was the very last point that I wanted to
9 comment about as well because, Frank, you had on your
10 summary slide the notion that the molecular pathogenesis of
11 childhood and adult cancers were different. That seemed to
12 imply that you were saying that if we saw a molecular
13 lesion in adults, that it may not make any sense to study
14 inhibitors of that molecular lesion in children. I wanted
15 you to comment on that because it seems sort of
16 counterintuitive. If you see overexpression of something
17 in breast cancer and you see overexpression of the same
18 thing in osteosarcoma, shouldn't you try the inhibitor of
19 that receptor?

20 DR. BALIS: Yes, I would certainly agree with
21 that. I think Malcolm's point is a good one. There may be
22 common pathways that are important for all tumors that
23 we'll be targeting that aren't necessarily involved
24 directly in the pathogenesis of those tumors but is
25 important in terms of maintaining them that may be

1 applicable to both types.

2 I was just referring to the fact that as a
3 general rule, if we become much more selective in terms of
4 where drugs act, that there are enough differences that a
5 drug that is important in terms of the way it works in
6 adult cancers may have no application in childhood cancers
7 because of the difference in pathogenesis. But I'm not
8 saying that if there are pathways that are in common that
9 we shouldn't study them.

10 DR. UNGERLEIDER: Will we have a chance to
11 discuss later on the notion that Susan Cohn mentioned this
12 morning about what exactly is the definition of indication?
13 Could it include molecular abnormalities?

14 DR. SANTANA: I think that's what the
15 discussion is going to be all about after the break. So,
16 with that, let's go ahead and take a 15-minute break and
17 reconvene at a quarter to 4:00.

18 (Recess.)

19 DR. SANTANA: We need to go ahead and get
20 started because some of us have flights to catch, and we
21 want to make sure that we have the discussion of the
22 questions. So, if people could take their seats.

23 I think Dr. Hirschfeld will have some
24 introductory comments again, and then we'll go directly to
25 the questions.

1 DR. HIRSCHFELD: I'm supposed to tell the
2 committee the charge. So, what we were interested in and
3 what we knew is that we would be lucky if we got to discuss
4 one of the questions today, but we wanted to give the total
5 overview.

6 I had divided the questions sort of into three
7 arbitrary groupings. The first would be to discuss some
8 general principles which addresses the phrasing of the
9 issue that Dr. Cohn presented to us this morning. Dr.
10 Ungerleider has been thinking about this, I know, for many
11 years. What are the general principles regarding the type
12 of evidence? That is, if we want to start thinking of
13 linking tumor types, should we be relying on histology,
14 cytogenetics, other types of markers, and how much
15 congruence do we need? That would be the general idea. If
16 we have a pathway that is altered in multiple tumor types,
17 but it's a common pathway, is that sufficient for us to be
18 considering linkages?

19 Then if there's any time today, we might
20 consider discussing some tumor types, and then definitely
21 in future meetings, we're going to be discussing some
22 issues regarding trial design.

23 Mr. Chairman.

24 DR. SANTANA: Let's go ahead and get started.
25 The first broad topic is this issue of general principles

1 of linking tumors. So, go ahead. You should all have your
2 questions in front of you. So, we'll try to address the
3 first one. The first question has some categorical
4 subparts, and we'll go through them one by one.

5 Consider the application of the following
6 diagnostic criteria to the general problem of describing
7 similarities between adult and pediatric tumors.
8 Recognizing the diversity of the various types of cancers,
9 what criteria would you use to consider them similar, and
10 would you consider each condition as necessary or
11 sufficient?

12 So, the first sub-question is, if the same
13 cytogenetic lesion is found in specimens from both tumor
14 types, would you consider that strong enough evidence to
15 lump them together? Comments?

16 I'll make a comment. I think if the
17 cytogenetic lesion tells us something about the biology of
18 the disease and if the cytogenetic lesion and the biology
19 reflect the same response to a given agent, then you could
20 link them. I think the example that I always think about
21 is 922 in CML. If it's the same in children -- I'm talking
22 about a cytogenetic lesion, very specific -- if it's the
23 same lesion in CML in kids as in adults, then
24 pathogenically it probably is the same disease, and if I
25 have an agent that responds in adults, it's very likely

1 | that there may be a response in a kid who has the same
2 | cytogenetic lesion. I'm just bringing a point of
3 | discussion.

4 | Susan.

5 | DR. COHN: I think it very much depends on what
6 | the lesion is. Obviously, there are some lesions that very
7 | much describe the pathogenesis, are involved with the
8 | pathogenesis of the tumor, and I think the 922 is certainly
9 | a paradigm for that type of abnormality.

10 | There are other abnormalities, though,
11 | cytogenetically that are relatively ubiquitous, such as a
12 | 1p deletion, for example. I wouldn't dare to say that if
13 | you have a 1p deletion in one tumor, that's the same thing
14 | as having the same kind of tumor and that, therefore, with
15 | the drugs that you'd use, you'd see similar responses. So,
16 | I think you have to be very careful, when you just kind of
17 | classify it as a cytogenetic lesion, as to exactly what
18 | that means.

19 | DR. SANTANA: David?

20 | DR. PARHAM: I think another danger of using
21 | strictly cytogenetics from the diagnosis standpoint and
22 | inclusion in trials can be illustrated by what's been
23 | happening with the IRSG in terms of alveolar
24 | rhabdomyosarcomas, which we stratified on a separate
25 | protocol because they are more aggressive tumors and

1 haven't responded historically. In fact, I think it was 30
2 to 40 percent of these initially were found to be negative
3 for the cytogenetic fusion, and if you use that criteria,
4 then you would have 40 percent that could have gone on
5 protocol that weren't.

6 Through time, we've managed to chip away at
7 that, where it's down to less than 20 percent for one
8 reason or another. It might have been that nested PCR was
9 more sensitive, or it might be that there's an alternate
10 fusion partner that was previously undescribed, or for
11 various reasons, technological and biological, there may be
12 related cytogenetics, but it's not evident. But the
13 histology tells you it's an alveolar rhabdomyosarcoma, yet
14 it takes a while for the biology to catch up with exactly
15 why it didn't have the classic fusion. So, I think that's
16 one of the dangers.

17 DR. SANTANA: But putting it the other way, I
18 guess to try to address the issue, if you had a 40-year-old
19 who had a rhabdomyosarcoma, who had the molecular marker --
20 let's even make it much broader -- of alveolar
21 rhabdomyosarcoma, could you lump those together?

22 DR. PARHAM: Yes, and I think that's the
23 reverse side of the coin that I see a real need for, and
24 that is inclusion of adults in these trials if they have
25 pediatric type tumors. I would say the answer to that is

1 | yes. I don't see a reason why not other than the reasons
2 | talked about earlier with the differences in response of
3 | children and toxicities with children. But biologically I
4 | would say, yes, that would be a good reason to do it.

5 | I'm just saying the reverse side of the coin is
6 | if you don't have a classic cytogenetic lesion and you have
7 | the histology, that doesn't mean the histology is wrong all
8 | the time. It may just mean that you haven't learned enough
9 | about the biology to understand why you didn't see the
10 | classic fusion.

11 | DR. HIRSCHFELD: I'd like to ask Dr. Burger if
12 | there are any applications in brain tumors where this might
13 | be applicable.

14 | DR. BURGER: They're not common. There's a
15 | very small percentage, maybe 4 percent of medulloblastomas
16 | with c-myc. There's ndm-2 amplification in some
17 | glioblastomas. There's EGFR amplification in the primary
18 | glioblastoma, but that's not a very common lesion
19 | apparently in children.

20 | DR. SANTANA: Any other further comments?
21 | Frank?

22 | DR. BALIS: I think one critical issue here is
23 | whether the therapy that we're studying is targeting the
24 | cytogenetic abnormality that we're looking at. Examples
25 | would be APL and retinoids. Is the fusion protein that's

1 formed by that cytogenetic abnormality the target of the
2 drug that we're looking at? I think in that situation it
3 makes sense to maybe disregard age. But if it's unrelated
4 -- and there are lots of cytogenetic abnormalities that
5 occur that may be peripherally related to the pathogenesis
6 of the tumor or its sensitivity to therapy that would not,
7 obviously, be applicable to conjoining adult and pediatric
8 patients.

9 DR. SANTANA: Jim?

10 DR. BOYETT: I think I'm confused. I thought
11 the discussion was about trying to decide where there might
12 be similar tumors in adults as children. I didn't realize
13 the discussion was about whether you could lump them and
14 treat them on the same trial.

15 DR. SANTANA: No, no, no. If you got that
16 impression from my comments, that's the wrong impression.

17 DR. BOYETT: It is similar so that we could
18 translate adult treatments to children more rapidly.

19 DR. SANTANA: Right, that's the point.

20 DR. HIRSCHFELD: Right, and we're also making
21 the assumption, which Dr. Balis referred to, that therapy,
22 we would hope, would be some way or another targeted,
23 although that's not exclusively the intent, but that was an
24 assumption.

25 DR. SANTANA: But I think the critical

1 | qualifier to answering this question is what Frank just
2 | stated, which is it really depends what the agent is
3 | targeting. If it's the same lesion and the agent is
4 | targeting the same lesion, then age is not an issue, and I
5 | think those trials can be conducted together I think is the
6 | answer to that question.

7 | DR. FINKELSTEIN: But I think you also have to
8 | add in Susan's comment. For example, if you have the same
9 | cytogenetic abnormality with Ewing's sarcoma, I would
10 | certainly accept that it's the same tumor. If your
11 | chromosome 11 is involved in a teenager and involved in a
12 | 29-year-old -- you don't have Ewing's sarcoma necessarily
13 | in a high incidence -- I'd say it's the same tumor.

14 | So, I agree with Frank, but I think Susan's
15 | comment is also important. I don't know how this committee
16 | is supposed to come to a consensus, but my suggestion is
17 | that both comments sort of tackle the question with what I
18 | think from my point of view is an acceptable answer.

19 | DR. SANTANA: Yes. I don't think we need to
20 | have a consensus on anything here. This is more of a
21 | discussion to help our colleagues in the agency try to
22 | understand these issues and how they're going to apply
23 | these principles in their decision making. So, I don't
24 | think we'll take a vote on anything here. I'm not going to
25 | take any votes.

1 David.

2 DR. PARHAM: Yes, I think that's a good
3 starting point to go with into fusions too, as well with
4 Ewing's sarcoma, because they're the same fusion. Yet,
5 within that group of fusion, there are two entirely
6 different types of prognostic indicators whether you have a
7 type 1 or a type 2 fusion. So, if you purely test for one
8 thing, then you're going to not see that there are actually
9 two groups of tumors from a biologic or at least from an
10 outcome standpoint.

11 So, I guess what I'm saying is it's always
12 risky to rely on one single parameter. Within that
13 particular group, if you said that's the same tumor because
14 it has the Ewing's translocation, that's not really true
15 unless you know the fusion type according to what we know
16 now with that particular biologic phenomenon.

17 DR. SANTANA: Yes. I think it's going to be
18 different for different tumors. In some tumors we're more
19 advanced in our knowledge of what these lesions mean and
20 potentially how the new drugs or the drugs we have
21 available affect those lesions, whereas in other tumors, I
22 don't think we have that knowledge yet, and it presents a
23 completely different issue in terms of how those studies
24 are done in kids versus in adults or in parallel or
25 separately or together.

1 Todd.

2 DR. GOLUB: I think there may be a tendency to
3 want to generate a single classification strategy that
4 either lumps or splits to some degree, and it is the
5 classification strategy for all agents, let's say, or for
6 all interventions. I think that that is unlikely to work,
7 particularly as you consider the future of molecularly
8 targeted therapies where there may be certain agents --
9 let's say, apoptosis inhibitors -- for which you may want
10 exactly to lump disparate types of tumors which share one
11 particular aspect of their pathophysiology, that is, their
12 mechanism of cell death response. Whereas, if you're using
13 a cell cycle checkpoint inhibitor, you may completely
14 change in a completely orthogonal direction the way that
15 you would classify these same tumors and now resplit them
16 and relump them in completely different dimensions. I'm
17 not sure that it's going to be successful to say Ewing's
18 sarcomas are forever linked to some other tumor based on
19 any single molecular characteristic.

20 DR. REYNOLDS: I just wonder if I could add
21 something to this list. It seems to me that if we start
22 with the principle of cancer, without splitting it, a
23 malignant disease with most likely metastatic potential,
24 what we're doing when we do the variety of methodologies,
25 whether it's histopathology, molecular genetics,

1 | cytogenetics, or looking at the age of the patient, is
2 | trying to do risk assessment, prognostic assessment. Also,
3 | we know from the history of chemotherapy, that a particular
4 | subgroup of these tumors will respond to agent X, whereas
5 | another group will not. It seems to me that the latter is
6 | the sole question we really should be focusing on, not the
7 | prognostic indications of the molecular genetics, but
8 | whether or not there's a similarity amongst these tumors in
9 | that they would respond or are likely to respond to a given
10 | agent. It seems that we have not listed on here the
11 | history of response.

12 | So, for example, if we have an adult tumor that
13 | has responded to cisplatinum, responded to etoposide, and
14 | these are effective drugs, and then a tumor that looks a
15 | little bit like it and behaves a little like it, but it's
16 | totally different in childhood cancer, responds to those
17 | same agents consistently, then isn't that a similarity that
18 | we should be taking into account here?

19 | DR. HIRSCHFELD: Well, that's exactly the point
20 | because you used the phrase "looks a little bit like it,"
21 | "behaves a little like it." That's where we're trying to
22 | get a little better definition on what's intended or how
23 | one can apply this idea of "looks a little, behaves a
24 | little like."

25 | DR. REYNOLDS: But looks a little and behaves a

1 little could still be totally different histologies,
2 different organs of origin, but still they are cancer, and
3 yet they're both responding to the same agents. So, I
4 wonder if maybe we should focus more on that and less on
5 trying to subdivide or lump on the basis of a thousand gene
6 array expressions. Really, it's response to agents that's
7 at issue.

8 DR. HIRSCHFELD: What we're trying to get
9 advice on is which principle should be used, and if the
10 recommendation or the discussion is that using cytogenetics
11 or histology or other markers is not informative, then that
12 would be also useful advice.

13 DR. SANTANA: Well, we haven't gotten there
14 yet. So, let's continue.

15 DR. HIRSCHFELD: No. I'm just saying that
16 everything is on the table, so to speak.

17 DR. SANTANA: Sue.

18 DR. COHN: Again, this isn't on your list here
19 because you're kind of looking at the tumor cells, and I
20 just again want to raise this whole more broad question of
21 if you listen to Judah Folkman talk, there are other cancer
22 cells, and then there are other cells in these tumors.
23 Specifically, the blood vessels are just one example of
24 cells that do contribute ubiquitously to tumor growth
25 across all sorts of different histologic tumors and also

1 across all sorts of tumors that have different molecular
2 and cytogenetic bases.

3 I think that if you do step back -- and it's
4 sort of going along with what Pat is saying in terms of
5 looking at response -- there are perhaps broad categories
6 of a variety of different agents that tumors will respond
7 to. I'm just wondering if perhaps that's what we ought to
8 step back and look at. There will be tumors that will have
9 specific genetic abnormalities that will certainly cross
10 pediatric and adult cancers. But more importantly, I think
11 there are other things that are very common to all of
12 cancer, and that would be relatively simple for us to lump
13 together and to look at together.

14 DR. HIRSCHFELD: Well, it doesn't really matter
15 which order we take it in, but that's one of the concepts
16 that we wanted to look at. We have tools at hand. How can
17 we use those tools? And then we have concepts like if we
18 have an angiogenesis inhibitor, then how should we apply
19 that?

20 So, I completely agree with the point of view,
21 and it's, I guess, up to Dr. Santana if we want to skip
22 around in terms of the order. But for those who don't have
23 the questions in front of them, we're just asking some
24 questions about specific techniques and when and how they
25 might be applied and then the more general question.

1 DR. SANTANA: I think we should go at least
2 through all of 1 and its subparts, and then after answering
3 that, revisit this issue, Sue, and I'll call upon you to
4 reintroduce it. Okay?

5 DR. COHN: Yes.

6 DR. SANTANA: So, I think you got some comments
7 about the issue of cytogenetics and how potentially that
8 could be used or not used and the pitfalls in using that.

9 The second one is the histochemical pattern.
10 If the histochemical pattern is the same, is it the same?
11 David, do you want to comment?

12 DR. PARHAM: Well, that one again, to use your
13 Ewing's sarcoma analogy as a stepping point, is one where I
14 think pathologists have devoted a lot of time and attention
15 to trying to see if it's important to separate Ewing's
16 sarcomas from PNETs if they're biologically the same tumor.
17 After much time and expense, I think it's common knowledge
18 in the United States that it doesn't make a difference.
19 Even though they have different histologies, they're still
20 biologically the same tumor. Now, that's still being
21 discussed in Europe, and it's still not completely put to
22 bed yet. Maybe it will never be.

23 But I think that I would not certainly say that
24 the histologic pattern should be the ultimate defining
25 thing either because there are lesions that have different

1 | histologies that are really the same. It's again a
2 | challenge. It's hard to make generalizations. It's easier
3 | to pick at the exceptions than the generalizations. It's
4 | easy to identify exceptions.

5 | DR. SANTANA: But, David, the issue is for
6 | certain tumors, we may have more information than
7 | histology. But there are some tumors that all we have is
8 | histology.

9 | DR. PARHAM: Right, and particularly the rare
10 | ones.

11 | DR. SANTANA: Right. So, in those situations,
12 | since histology is the only valid variable that we have in
13 | terms of the study design of the drugs that are going to be
14 | tested, I guess the answer is very logical, if you use
15 | logic. If that's all you have, that's all you have.

16 | DR. PARHAM: I think particularly when you deal
17 | with these rare things like non-rhabdosarcomas where there
18 | are so many different histologic types -- and I think my
19 | list is probably about as long as yours, Peter, although
20 | it's tough -- then I think it's really imperative to find
21 | things like we've done with the grading system to try to
22 | get a handle on things that are alike because, otherwise,
23 | it's impossible to do a study.

24 | Again, I'm not saying that we should go with
25 | histology. I think we need to take a broader view.

1 DR. SANTANA: Peter?

2 DR. BURGER: I think histology certainly has
3 its worth, but I think we should be very careful to not
4 make the assumption that the term means the same to all
5 pathologists. You can use the term "glioblastoma," for
6 example, but it encompasses a rather broad range of
7 lesions. They fit certain criteria, but when you look at
8 the spectrum, you would pretty soon realize that this has
9 some things in there that might be outliers.

10 Histology has to be precise and defined in some
11 way before it's accepted as meaning something. It cannot
12 be the diagnosis that would be made by multiple
13 pathologists across the country.

14 DR. SANTANA: So, in some of those very
15 critical studies, are you then advocating central review to
16 make sure that the population is well-defined?

17 DR. BURGER: Yes, right.

18 DR. PARHAM: I think I would have to stay with
19 central review.

20 DR. SANTANA: Steve.

21 DR. HIRSCHFELD: I would just like to ask, if
22 any of these cases, if there is an outlier, an exception,
23 where you think it might apply, then that would also be
24 informative.

25 DR. PARHAM: Well, again, if you look at

1 rhabdomyosarcomas, it's obvious there are two different
2 groups. I think a lot of the things we define are because
3 of the outliers. Now we're finding if you have different
4 fusions, they do differently as well. So, I think our
5 knowledge progresses because of the outliers in terms of
6 biology and histology. But we keep dividing the pie up
7 thinner and thinner in terms of the numbers is the problem,
8 and also it becomes more and more difficult to acquire the
9 necessary number of cases if we are also, at the same time,
10 decreasing the amount of tissue we have to study.

11 DR. SANTANA: Jim?

12 DR. BOYETT: A comment about the central
13 review. One of the things I'd want to make sure of is if
14 we used the central review to define a patient population,
15 that that patient population is well-defined and is not
16 based on the bias of who the central reviewer is. As in
17 your example, Peter, you gave in your talk of the three
18 neuropathologists reviewing it, when two of the three of
19 you agreed, then there was certainly something different
20 about the tumors. So, I think we have to be cognizant that
21 experts do disagree with one another, and if they're used
22 as a central review, depending on who the expert is, you
23 may be looking at a different population of patients.

24 DR. SANTANA: A point well taken.

25 Any further discussion?

1 DR. PARHAM: I think the biggest hang-up I've
2 seen with central review -- Peter may have the same comment
3 -- and that is the politics. That is, if I get a case from
4 a certain pathologist, say, for example, Dr. Pepper Daner
5 who's a noted expert, and I disagree with him, I have a lot
6 more problem making my own opinion than I do if it's
7 somebody from Bug Tustle, Arkansas. So, the biggest
8 problem with central review I think is the peripherals, not
9 the major issue of what you think the tumor is, but the
10 peripheral issues.

11 DR. SANTANA: Peter?

12 DR. BURGER: Well, I've really not had the
13 political problems you have, but I think the problem is
14 that even the central reviewers, as Jim has alluded to, can
15 have vastly different experiences and criteria for things.
16 I'm thinking particularly of the pediatric brain tumors.
17 Malignant gliomas would be the best example. It's a very
18 heterogeneous group. I'm not sure there's any easy way to
19 sort these out by consensus. I think you probably need one
20 person that is experienced in that area and go with that
21 because you get into a committee format, you will quickly
22 have rather chaotic reviews. But that's not the way it's
23 done. It's done by consensus, but I'm not convinced that's
24 always the best.

25 DR. SANTANA: Frank?

1 DR. BALIS: I hate to the one who states the
2 obvious consistently, but the one thing I think we've
3 learned from treating cancer over many years is that
4 histology alone doesn't tell us that patients are going to
5 respond or not respond to therapy.

6 I view rhabdomyosarcoma as an example. A
7 patient with metastatic rhabdomyosarcoma, who has the same
8 tumor under the microscope, has a very different prognosis
9 and response to therapy than a patient who has a localized
10 tumor. So, although it helps us to classify, there's a lot
11 it's not telling us about the biology and specifically
12 about responsiveness to therapy that I think may not make
13 it the best thing to use to decide whether adult and
14 pediatric patients are the same, and we can't do that
15 within a population of patients.

16 DR. SANTANA: Well, I think the other good
17 example is ALL. ALL under the microscope in adults look
18 the same as ALL under the microscope in kids. It's the
19 whole biology that's different and therefore the response
20 to therapy.

21 Have we covered that one enough? Have we
22 beaten that one down enough?

23 DR. HIRSCHFELD: I think so. Most of the
24 questions were not designed to necessarily be easy. They,
25 in fact, were intended to be somewhat provocative so that

1 we could have this discussion because, as far as I was able
2 to determine, looking through the literature, no one has
3 had this discussion before.

4 DR. SANTANA: So, with that, let's tackle the
5 third one. If a molecular marker, such as an expression of
6 an oncogene, is the same. Sue?

7 DR. COHN: Well, again, I think that I would be
8 voting negatively on this one as well. I think
9 overexpression of oncogenes means different things in
10 different situations. I'll give you an example, and that
11 is just with n-myc and neuroblastoma. If the gene is
12 amplified and therefore you have overexpression of the gene
13 subsequent to amplification, that certainly is associated
14 with the worst outcome for those patients. However, there
15 have been some studies that have demonstrated that if you
16 have overexpression of n-myc in situations where the gene
17 is not amplified, that is not necessarily prognostic.

18 There have also been studies that have
19 demonstrated that c-myc overexpression in colon cancer and
20 breast cancer is actually associated with a better outcome.
21 This may be in total contrast to amplification. So, just
22 looking at expression, I don't think is necessarily the way
23 to go.

24 DR. HIRSCHFELD: Just to clarify, the oncogene
25 overexpression was intended as a paradigm for the broader

1 class of using a molecular marker. So, your comments were
2 important specifically with regard to that, but there might
3 be other circumstances which we might want to consider.

4 DR. COHN: Well, again, if you want to take the
5 analogy with small lung cancer, I think there you certainly
6 can draw some parallels between amplification of, for
7 example, n-myc or c-myc or l-myc that take place in small
8 cell lung cancer and many of the biologic characteristics
9 that we see with neuroblastoma.

10 But as I said, I just think each one of these,
11 as an individual lesion, you need to consider very
12 carefully because it depends upon sort of like the
13 cytogenetic lesion. If the cytogenetic lesion is truly
14 what is involved in the pathogenesis of the tumor and your
15 drug is specific for that cytogenetic lesion, then it all
16 makes a lot of sense. If it is not central to the
17 pathogenesis of the tumor, but rather just associated
18 because there's more rapid proliferation associated with
19 certain oncogene expressions or lp deletions, but it's not
20 central to pathogenesis, then I think that that's a totally
21 separate issue.

22 In addition, if your drug that you are looking
23 at isn't perhaps at all related to that particular lesion
24 or isn't directed toward that particular lesion, then it
25 also, I don't think, makes a lot of sense to look at that

1 | in making your decisions.

2 | DR. BURGER: Is this something that's been
3 | studied systematically, and if not, shouldn't it be? It
4 | seems it's an obviously question whether the same genetic
5 | abnormality in different tumors would be a target of
6 | therapy whether it's the only target or not. Has someone
7 | done this? Are there funding mechanisms to study this
8 | issue? It would be a perfect chance for --

9 | DR. HIRSCHFELD: Yes. I'll let Malcolm address
10 | that in more detail, but I know that, for instance, there
11 | are a number of commercial ventures which are looking at
12 | modifying the expression of p53 or using gene therapy or in
13 | some ways looking at downstream pathways of p53 because
14 | it's so broad. So, the short answer is, yes, it's been
15 | thought of, and whether it's been systematically examined
16 | or adequately examined I think is far more open.

17 | Do you want to comment, Malcolm, now that I've
18 | put you on the spot?

19 | DR. SMITH: Well, I don't know of any specific
20 | funding programs. Although taking the ras mutation
21 | example, ras mutation occurs frequently in pancreatic
22 | cancer. Ras mutations occur in some percentage of juvenile
23 | myelomonocytic leukemia, or JMML. The context of what that
24 | ras mutation may be doing in those two tumors and how it
25 | would respond to a ras directed therapy may be very

1 different because it's in the context of a different
2 cellular milieu. It doesn't mean that it's not interesting
3 to think about looking at the same type of drugs in these
4 two cases, and people are looking at things that interdict
5 the ras pathway in both of those cases.

6 DR. REYNOLDS: I thought of an example of an
7 agent that we don't have yet but one that might become
8 available that I think would be broadly distributed across
9 all cancers and that is telomerase inhibitors. If someone
10 does come up with an effective telomerase inhibitor, since
11 telomerase is activated in a high proportion of both
12 pediatric and adult cancers, why wouldn't they be
13 considered the same for the purpose of studying that
14 particular drug?

15 DR. COHN: I just want to second what Pat is
16 saying. I really think that's where I can see very easily
17 you can lump tumors together, when it comes to specific
18 pathways, whether it's telomerase or apoptosis or
19 angiogenesis, where there are pathways that are ubiquitous
20 to all the tumors. I think that is much more likely for us
21 to be able to make a case for those types of agents to be
22 tested very quickly in the pediatric population, rather
23 than looking at specific abnormalities in some of these
24 molecular lesions, which I agree with Malcolm, I think have
25 different effects depending upon the cellular milieu.

1 DR. HIRSCHFELD: But let me take that just one
2 step further. If we are in a state where we have
3 insufficient knowledge, should we ask the question, or
4 should our default state be we have insufficient knowledge,
5 and therefore we shouldn't ask the question, and the
6 question being, in terms of in a regulatory sense, you
7 ought to study this in children.

8 DR. REYNOLDS: I'd like to explore your
9 question a bit more.

10 DR. HIRSCHFELD: Yes, sure. If we're at a
11 point -- and I'll take the example that Malcolm gave where
12 we have a ras mutation in pancreatic cancer and in juvenile
13 monocytic leukemia, and we have a therapy that's directed
14 against ras, should we say, well, there are two lesions
15 where we have a molecular target. You have a therapy
16 directed at that target. We think you ought to do a study
17 in pediatrics in juvenile monocytic leukemia because you
18 have a directed therapy. Or should the default state be we
19 don't know enough about the context of ras overexpression,
20 and therefore there's no need for you to make this
21 available for pediatric studies or to study it in this
22 case? Frank.

23 DR. BALIS: I think the way that we're going to
24 learn about the importance of these is maybe through a
25 therapeutic approach. It may be backwards, but that's the

1 way we learned about how retinoids worked in APL by trying
2 them and seeing if they were effective and then looking at
3 why.

4 But I think the other part of it -- and what
5 people are saying here -- is that it may not be a molecular
6 lesion but a pathway that we ought to be looking at and all
7 parts of that pathway, which we probably don't know enough
8 about yet, but I think we're close to that. If we can
9 define which pathway is important, maybe there are multiple
10 lesions in that pathway. That's what we ought to be
11 targeting.

12 DR. FINKELSTEIN: Are you asking the question
13 in terms of the scientific validity of the question, which
14 is should we be exploring this avenue for the new
15 millennium of drugs, or are you specifically referring to
16 FDAMA?

17 DR. HIRSCHFELD: FDAMA doesn't play a role in
18 this. I'm trying to look at it at the Pediatric Rule and
19 how we might interpret it. Scientifically there are many,
20 many interesting questions which all of us would like to
21 know answers to. The question is, should we invoke a
22 regulatory tool in order to have a study at least
23 contemplated, if not performed, or should we say we have
24 insufficient knowledge and we should just withhold making a
25 recommendation or trying to invoke the regulatory tool?

1 DR. SANTANA: So, that's an area you would give
2 a waiver.

3 DR. HIRSCHFELD: Right, right. So, it would
4 say it would give a waiver.

5 DR. FINKELSTEIN: I think everyone would agree
6 that it would be an interesting question to ask. I'm not
7 quite sure how the implementation takes place, and for that
8 I'd have to leave it to those of you who have more
9 experience, namely, an FDA, an NCI, a Pediatric Oncology
10 Group.

11 DR. PAZDUR: I think the situation here is this
12 is an interesting question. It has to be validated from a
13 scientific point. Then after it is validated, then you
14 could take the hammer of the rule and say you must do this.
15 But you cannot use a regulatory principle to try to force a
16 scientific question to be answered. That scientific
17 question needs to be answered from a scientific
18 perspective. You have an interest in it. Does this
19 correlation exist. Once that correlation does exist, then
20 you could make companies study it once you have established
21 that relationship that exists I think.

22 DR. HIRSCHFELD: But that's assuming that you
23 have independent means, and I think paradigm that Frank
24 Balis brought up is that sometimes using therapies is a
25 direct way to open the door to other studies.

1 DR. PAZDUR: I think you could encourage them
2 to do it, but mandating them to do it is a different aspect
3 here because if you were on the other side of the equation
4 here and from a company's perspective to be required to do
5 something is a much different thing that is this an
6 interesting scientific question that needs to be studied.
7 The interesting scientific question needs to be studied.
8 That link needs to be made. Once that link is made, then
9 you can exert a regulatory authority over it.

10 DR. SANTANA: It's a little bit like which
11 comes first. The chicken or the egg? If the company is
12 coming to you and saying, I want an indication of compound
13 X for adults who have this ras mutation in this particular
14 group of diseases, they are the ones who are requesting the
15 indication. Right?

16 DR. PAZDUR: But usually indications are not
17 written in that fashion. The indication would be written
18 or a specific disease. Obviously if the indication is
19 written in that fashion --

20 DR. SANTANA: But that's the point Sue I think
21 was trying to make earlier.

22 DR. PAZDUR: If you're writing an indication
23 for a molecular lesion here, yes, then it would occur.
24 Then that would be reasonable. But for where we stand now,
25 most of the indications are for the treatment of first line

1 breast cancer or prostate cancer or a histological
2 diagnosis. I think it would be somewhat tenuous on our
3 part, just because we have a suspicion that a molecular
4 change may be related between diseases, to say you must do
5 this on very tenuous scientific grounds before it's proven.

6 DR. HIRSCHFELD: So, we'd start the day with
7 the default state that will ask for nothing because we say
8 pediatric tumors are different than adult tumors. What
9 we'd want to see is if we end the day by saying, okay,
10 we'll continue to ask for nothing, or are there areas or
11 conditions which should provoke in us a reaction to say,
12 well, we think you should ask for something?

13 DR. PRZEPIORKA: Actually I want to disagree
14 with Rick about not doing something just because
15 molecularly it looks the same. I think, for example, with
16 the new tyrosine kinase inhibitor Aresa out there for lung
17 cancer, we're learning more and more about tyrosine kinases
18 in all cancers. If we really wanted to get these drugs
19 into the hands of the pediatric oncologists as early as
20 possible, then just because there's no lung cancer in
21 children, if there are other malignancies that have EGFR
22 receptors on them and in vitro if there's evidence that
23 these drugs inhibit growth of those pediatric tumors in
24 vitro, then I think there is a good reason to invoke the
25 Pediatric Rule and make the drug companies test those drugs

1 | in the pediatric patients.

2 | DR. PAZDUR: I think you have to look at this
3 | on an individual basis, and it results from what the actual
4 | science is and the strength of that science to make that.
5 | But once you start requiring people to do something, that
6 | is a much different situation than this is an interesting
7 | scientific question that we want answered. That's the
8 | point I'm trying to make here. The scientific link has to
9 | come first before a regulatory enforcement and policy can
10 | happen. That's the issue. It probably has to be done on
11 | an individual basis.

12 | DR. HIRSCHFELD: But then again, what we'd like
13 | some advice on is what kind of science would be needed. If
14 | we know that pancreatic tumors have ras which is important
15 | for maintaining the tumorigenic state and we suspect that
16 | juvenile monocytic leukemia uses ras to continue the
17 | tumorigenic state, is that something which we should
18 | consider as an adequate scientific basis?

19 | DR. REYNOLDS: I just wondered from the FDA's
20 | standpoint if it was not possible if there was such an
21 | agent, for example, that hit a broad spectrum of targets
22 | that might be present in pediatric malignancies, if you
23 | could then require, or at least encourage, the drug company
24 | that's submitting the IND to provide that agent for
25 | preclinical studies that might define whether or not it

1 | would have some potential activity in pediatrics, and based
2 | upon those preclinical studies, if they were very
3 | promising, at least encourage, if not require, under the
4 | rule a pediatric study.

5 | DR. HIRSCHFELD: That's an interesting thought.
6 | The difficulties are, one, we don't have really much
7 | leverage with preclinical studies because we regulate
8 | clinical studies.

9 | The second is that we always encourage, and
10 | that's what we've said many times before. When anyone
11 | comes to visit us, they go home with a shopping bag and a
12 | brochure that says, study this in children.

13 | DR. PAZDUR: And I think also we're kind of
14 | putting the pharmaceutical industry in a dim light here.
15 | Why wouldn't they have an interest in looking at this also?
16 | Because obviously it would increase their market, their
17 | opportunity to look at drugs. I think that they have an
18 | interest also in expanding their portfolio to get a
19 | scientific basis of how their drug may work. So, hopefully
20 | these things will be done in concert rather than using some
21 | type of a regulatory hammer on the industry in a sense.
22 | Here again, it depends on the science here and how founded
23 | the scientific relationship is between this basically
24 | surrogate marker that you're using here.

25 | DR. REYNOLDS: Well, getting the agents in the

1 | lab has been a problem for a lot of us. So, I agree with
2 | you it's something that should be happening, but it's not.
3 | That's one of the reason we're raising this issue, is how
4 | can we encourage it to happen.

5 | DR. BALIS: In a sense, I think it's a shame
6 | that biologics weren't included in the rule because I think
7 | they'd serve as a great model. I think for many of the
8 | monoclonal antibodies, the indication is for a tumor that
9 | expresses a certain antigen, and there are pediatric tumors
10 | that express those same antigens. What is the response
11 | going to be as we demonstrate that, particularly when these
12 | drugs are still in their exclusivity phase, as to whether
13 | those studies are going to be required? The example I
14 | guess would be with osteosarcoma and herceptin. Are you
15 | requiring studies be done?

16 | DR. HIRSCHFELD: Well, right now our default
17 | state is we require zero. Nothing. We've heard the
18 | message that everyone would like to have new agents made
19 | available and that it's hard to get your hands on them.
20 | What we're trying to get a handle on is when and how can we
21 | invoke some leverage. So, one way we have that is if we
22 | invoke the Pediatric Rule which would mandate that studies
23 | be done. Then what would trigger that? That's, in
24 | essence, what we're asking for advice on.

25 | DR. SANTANA: Well, the science would trigger

1 | it because I would come to you and I would say this antigen
2 | is expressed in X tumor in kids, and I want to make sure
3 | that the company helps me do that study. That's what would
4 | trigger it.

5 | DR. HIRSCHFELD: So, then going back just to
6 | our questions again, if we have a molecular marker, i.e.,
7 | an antigen, that is expressed in osteosarcoma and there's a
8 | product available, drug or biological, that targets that
9 | antigen, should we then be saying you must make this
10 | available to pediatric investigators?

11 | DR. SANTANA: In the context, if the science is
12 | behind that to support it, that this condition, this
13 | expression of this antigen, also exists in pediatric
14 | tumors. Because you really can't force the companies to do
15 | something that has no scientific validity to it.

16 | DR. HIRSCHFELD: Absolutely the case. So, we
17 | would all agree that if the science supports it, but what
18 | should then be used for criteria for "if the science
19 | supports it"?

20 | DR. SANTANA: Does anybody want to address
21 | that?

22 | DR. BALIS: I think that the reason that these
23 | monoclonal antibodies are being approved is not because
24 | it's breast cancer. It's because the breast cancer
25 | expresses an antigen that the antibody is directed to. So,

1 | it's not the underlying histology that's important. It's
2 | the antigen that's important. And if that's the case, then
3 | if the antigen is expressed on other tumors, regardless of
4 | their histology, it ought to be studied.

5 | DR. HIRSCHFELD: Is that a point of view that's
6 | shared among people on the panel, that if you have, for
7 | instance, an antigen -- or I'll try to paraphrase Dr.
8 | Cohn's comment earlier -- if you have an enzyme or a fusion
9 | protein that is thought to be central to the pathogenesis
10 | of the tumor, that that would be a circumstance where if
11 | two tumors share that, that we should then say that this
12 | agent should be made available for pediatric tumors that
13 | share that characteristic or these characteristics?

14 | DR. SANTANA: I think the consensus is yes.
15 | Donna?

16 | DR. PRZEPIORKA: With one small caveat. I
17 | think if someone brought you a new drug and said, oh, look,
18 | it targets receptor X, let's do a clinical study, everyone
19 | would say, well, how do you know it's going to do something
20 | good rather than something bad? So, we have a series of
21 | tumor lines out there, when treated with Rituxan, actually
22 | ends up being a growth factor rather than an inhibitory
23 | factor.

24 | So, if you do go and extrapolate from the adult
25 | to the pediatric tumors based just on having a receptor

1 | there, I would still suggest that you might need to see
2 | some in vitro data showing that you're going to do some
3 | good and it's going to have the same mechanism of action in
4 | this tumor setting as it is in the adult tumor setting when
5 | it was tested in same way in vitro.

6 | DR. HIRSCHFELD: There's some one assumption
7 | and that is that there's a correlation between the in vitro
8 | model and the specific pediatric tumor.

9 | DR. SANTANA: Yes. We all recognize the
10 | limitations of the preclinical models, but the point is
11 | that the preclinical model would justify carrying out the
12 | study.

13 | DR. REYNOLDS: To amplify on that, again there
14 | are limitations to preclinical models, but that is data
15 | that I think contributes to our knowledge base and allows
16 | one to make better decisions than having no data at all
17 | with respect to pediatric tumors. And there are a lot more
18 | pediatric tumor cell lines than there are pediatric
19 | patients available to do these kinds of tests.

20 | (Laughter.)

21 | DR. HIRSCHFELD: And a lot more mice too.

22 | DR. SANTANA: Malcolm?

23 | DR. SMITH: I think it's an interesting idea to
24 | talk about being able to identify a need based on the
25 | target. For example, we do have to be careful, though, in

1 terms of the number of patients that are available with
2 that particular target, and as we go forward, in some ways
3 to echo the point Susan Weiner was making this morning,
4 there are limited numbers of patients and this particular
5 antigen on this particular cell may not be addressing the
6 most critical unmet need of all the unmet needs for
7 Burkitt's lymphoma or for ALL or for osteosarcoma even
8 though there is a monoclonal antibody that binds to an
9 antigen that's expressed from one or the other cells.

10 An example would be rituximab. In spite of
11 efforts in trying to get studies of this agent in children,
12 with the high cure rate and with the competing alternative
13 therapies, there's not been a great deal of enthusiasm for
14 proceeding with that kind of evaluation to this point in
15 time.

16 DR. HIRSCHFELD: Right. The rule specifically
17 states -- and now we're getting into the regulatory aspects
18 -- that there has to be either an adequate number of
19 patients, which is 50,000, which doesn't apply ever, or it
20 has to be considered a therapeutic advance. So, there are
21 two steps. One is should we trigger our thinking about the
22 rule, and that's what we're trying to discuss this
23 afternoon. And then once our thinking has been triggered,
24 then comes this judgment call as to whether it's a
25 therapeutic advance and would apply and if there's a

1 | medical need.

2 | DR. FINKELSTEIN: I'd like to address the
3 | latter because we have a unique situation in pediatric
4 | oncology. We really do have sessions where the FDA, the
5 | NCI, the public, the pediatric oncologists, the cooperative
6 | groups all sit down in a room. I would hope that if we
7 | kept that kind of approach with this kind of challenge,
8 | then that would help with the priority in terms of a
9 | national consensus.

10 | DR. SANTANA: I'm trying to address Malcolm's
11 | point. Is it really a matter of competing priorities for
12 | the example of the antibody that you gave, or is it that we
13 | haven't figured out where we're going to use it? Because
14 | clearly, I would say that the therapy of AML is still
15 | suboptimal. We don't cure 100 percent of the kids.

16 | So, the challenge for us to give assessment to
17 | the FDA and to you guys at the NCI is we haven't figured
18 | out where we're going to use it, how we're going to use it.
19 | Because we can't use it as a single drug. We could. There
20 | may be models where we could do that. Do you see the
21 | point?

22 | DR. SMITH: Of course, I was talking about the
23 | high grade lymphomas where CD20 would be expressed.
24 | Certainly for AML, Mylotarg would be an example of an agent
25 | targeted toward what clearly is an unmet need in pediatrics

1 that is better therapy for AML. In looking at the targeted
2 therapies and whether there is a need for a pediatric
3 study, it really is predicated on what the current therapy
4 is, what the success of that therapy is, and what the
5 competing priorities are for the limited numbers of
6 patients that can be studied in phase II and phase III
7 studies.

8 DR. HIRSCHFELD: And the implementation of that
9 would be that even if the molecular defect or the pathway
10 or whatever of model we're using, the cellular structure in
11 cases of telomeres, might apply, there's that second step
12 of deciding whether it meets an unmet medical need, which
13 would then result in us stating that the study is mandated
14 or not.

15 DR. SANTANA: We'll take one final comment from
16 the gentleman in the audience. Could you please identify
17 yourself and come to the front?

18 DR. GOOTENBERG: I'm Joe Gootenberg and I'm
19 from Biologics. I wanted to make a few comments about this
20 discussion that's going on right now.

21 The first is that the rule, which applies to us
22 -- and we've talking about things here which are biologics
23 -- is only triggered under certain circumstances. This has
24 gotten a little far away from it. If I'm right about this
25 -- and Steve, you can tell me -- the rule is only triggered

1 | if a company requests a waiver during its development or if
2 | they submit an application for an indication. We can't go
3 | back in time for a licensed drug and ask for the rule to be
4 | applied in that situation. Nor can we early in a drug's
5 | development come to them and say, oh, we're going to apply
6 | the Pediatric Rule to you, so you better start making plans
7 | for that. It's only triggered in those two situations.

8 | DR. SANTANA: Is that correct? The actual
9 | Pediatric Rule and the mandate, not the exclusivity, the
10 | other stuff. When a company comes to you early on in the
11 | process and they start presenting studies to you for an
12 | ultimate indication, because they do that early on, is that
13 | when you're going to invoke the rule?

14 | DR. HIRSCHFELD: Yes, actually we could because
15 | if we're using this paradigm of being independent of
16 | histology and rather looking at the pathway, they're going
17 | to eventually market their product based on a claim such as
18 | inhibits binding to her-2 neu or whatever that might be.
19 | So, we know whatever studies they're going to do, their
20 | marketing claim will be this is an inhibitor of her-2 neu,
21 | and therefore we can anticipate --

22 | DR. GOOTENBERG: Right. It will be tied to the
23 | indication that they ask for, that they claim. But if we
24 | can't know exactly what that indication will be when it
25 | becomes mature and it comes to the time, we can't exactly

1 target it.

2 On the other hand, maybe we can, if it's
3 absolutely know because it's tied to the indication. What
4 we're saying here is that we will take that part of the
5 indication and expand it out. I still, from a biologics
6 viewpoint, think from the company's viewpoint, they're not
7 going to really be happy with this unless we do it at the
8 time when they request a waiver or they really come to us
9 requesting that indication because before then, it doesn't
10 exist really.

11 DR. HIRSCHFELD: Well, that's a question of
12 timing then. But I think early on, if we follow the
13 recommendation that I'm hearing from our panel, that we
14 could inform them that when the time comes to file, that
15 they will have to answer this.

16 DR. GOOTENBERG: I think you're right about
17 that.

18 DR. HIRSCHFELD: And they may as well start
19 making plans now and talking to the cooperative groups or
20 pediatric investigators or whomever it is.

21 DR. GOOTENBERG: It's clear in biologics now
22 that indications are being sought like that for breast
23 cancer which is such-and-such positive or this or that, and
24 it's a narrow indication. You might have that handle.

25 Another one I want to throw in is for

1 | supportive care. Someone just brought up the idea here
2 | that our treatment of AML is less than optimal, and one of
3 | the problems is extreme toxicity. In fact, as Malcolm
4 | reminded me the other week, the last CCG AML protocol had
5 | to close because of excessive toxicity, and it was GI
6 | toxicity.

7 | And I'm not allowed to divulge any details
8 | here. What if a company came with not a disease directed
9 | but a symptom directed -- so fungal infection mucositis,
10 | biologic in this case -- which they're applying to another
11 | disease in adults over here, would we be able to say, well,
12 | we're not going to give you a pediatric waiver on that
13 | entity because we know that it could be used in childhood
14 | AML and probably really make a significant contribution to
15 | the cure rate of that? That's pretty tenuous, but that's a
16 | question we're going to have to face.

17 | DR. HIRSCHFELD: Well, that's exactly the kind
18 | of advice we're trying to seek. Can we invoke some basis
19 | other than histology in order to make the links?

20 | DR. SANTANA: Actually if I could quote some
21 | history here, I was involved with some of the trials that a
22 | particular company did with a cytokine that's now been
23 | commercially available for over 10 years, and I remember
24 | the discussions at that time. If it hadn't been because
25 | there was some pressure put upon them when they went to the

1 FDA for the indication in the absence of pediatric studies,
2 somebody had to put pressure on them to actually get those
3 studies done. Now that drug is widely used in pediatrics,
4 maybe not with adequately documented studies, but it's
5 still widely used in pediatrics, and I think it has been of
6 advantage to some patients.

7 So, the point is that even for supportive care
8 indications, the FDA has to look whether those indications
9 also apply to children, and if they do, then I think my own
10 opinion here -- it's just my opinion -- is that you would
11 have to invoke the rule.

12 DR. REYNOLDS: If I could just ask for one
13 clarification, which I think addresses a point that Sue
14 raised this morning, and that is if somebody comes to you
15 and asks for a waiver and you say, no, we think that this
16 molecular entity targets something that's going to be
17 common in pediatric cancer, we're not giving you a waiver,
18 we think you should deal with pediatrics, and then in the
19 context of doing the science of looking at that, when they
20 talk to the cooperative group and involve CTEP and
21 everybody, and everybody looks at it and says, you know, we
22 don't really think this should be studied in pediatrics now
23 or it shouldn't be studied at all, one of the two, then you
24 could certainly go back and still grant a waiver, couldn't
25 you? So, it's not an all-or-none or irrevocable thing.

1 DR. HIRSCHFELD: This is true. Hopefully we
2 would be talking to our colleagues in CTEP and the
3 cooperative groups, et cetera in terms of making the
4 determination.

5 The underlying principle, though, is again we
6 started the day with the idea that we would not ask anybody
7 for anything, and where we want it to now come to is maybe
8 we should be asking people for some things. Then we can,
9 on a case-by-case basis, as Dr. Pazdur said, decide whether
10 it would be applied, but at least we'd have some principles
11 to follow.

12 DR. REYNOLDS: Right. Because if you start the
13 way that you began, then there's no impetus, there's no
14 pressure moving things toward the cooperative group to
15 really consider the pediatric possibilities early on. But
16 if you take the more forceful approach that we're moving
17 toward, then there is that and there's more opportunity for
18 decisions to be made.

19 DR. SANTANA: Jim, we'll take one last comment
20 on this question, and then I want to cover the question of
21 the microassay and then we'll stop there. So, Jim.

22 DR. BOYETT: Actually there are other entities
23 out there other than the cooperative groups who are capable
24 of doing studies and have done studies for a long, long
25 time. So, when I hear this discussion, it seems to say

1 that the only people who are going to be approached are the
2 cooperative groups. I think there are other ways to manage
3 that.

4 DR. HIRSCHFELD: That certainly wasn't
5 intended. We try to cast a wide net in terms of whom we
6 discuss and consult with, as you can tell by looking at the
7 makeup of this committee.

8 DR. SANTANA: Actually Malcolm did refer a
9 little bit to that this morning when he talked about the
10 CTEP process where there are other teams or other groups
11 that helped sort this out in terms of project grants or
12 academic centers, et cetera.

13 I'd like to move on and then just finish with
14 this issue of the microarray displays and how those
15 potentially could be utilized. There are actually three
16 points to this question. They're all linked together, so I
17 think we'll just take them as a group.

18 Is there insufficient collective experience to
19 make a recommendation regarding the use of this new tool?
20 Should it be used as supporting evidence in addition to
21 other criteria? If the displays are within some predefined
22 tolerance, sufficient evidence is available without
23 confirmation by other techniques. The bottom line is, how
24 can we use this technique and are we ready to bring it to
25 prime time in terms of studies?

1 Todd, do you want to address that?

2 DR. GOLUB: I don't really see the microarrays
3 being fundamentally different from any of the other
4 criteria, including histologic criteria or other molecular
5 markers. I think each of these ways of looking at tumors
6 needs to be looked at collectively for individual tumors
7 with different weights being given to these different
8 parameters, depending on their sensitivity, specificity,
9 and degree of experience in testing in the field. I think
10 it would be a mistake to try to summarily include or
11 exclude any one particular methodology for any one
12 particular tumor.

13 One question that I guess I'd like to just pose
14 would be regarding the Pediatric Rule. What if, let's say,
15 ara C were coming to the FDA now? You say, well, nucleic
16 acid synthesis is important for adult tumors and we can
17 prove that you need nucleic acid in childhood malignancy as
18 well. This a universal target. Should the rule be
19 invoked?

20 DR. HIRSCHFELD: And the answer, based on the
21 sage advice we've heard this afternoon, is that it
22 apparently is not endemic to the pathogenic process of the
23 tumor involved, that it would be a general metabolic
24 inhibitor, and therefore, we wouldn't in that case feel
25 that we would be compelled to trigger the rule.

1 DR. GOLUB: So, then you're only interested in
2 molecules that target proteins that are involved in the
3 pathogenesis, even if you can absolutely -- so, telomerase
4 would not apply in that case where a mutation in the
5 telomerase pathway itself probably is not what's going to
6 be targeted by these molecules, but if you can turn off
7 telomerase activity, let's assume that you can stop all
8 tumors dead in their tracks. Are you saying that would not
9 apply?

10 DR. HIRSCHFELD: Well, I'm trying to capture
11 what I thought the advice might be, but I think we would be
12 open to essentially any specific advice.

13 My personal opinion would be that if you have a
14 pathway -- and certainly even if you're not targeting
15 telomerase directly but some other element in that
16 signaling pathway or that feedback loop -- that one might I
17 think make the argument that this was necessary for
18 maintaining the tumorigenic state. If one goes into a more
19 generic metabolic process like DNA synthesis or protein
20 synthesis or membrane synthesis, then I think it becomes
21 one step further removed.

22 I think we've already moved from going to no
23 recommendations to making a recommendation based on having
24 a pathway which can be identified as being essential for
25 either tumorigenesis or tumor maintenance.

1 DR. GOLUB: I'm not sure I see the distinction
2 there. So, an angiogenesis inhibitor then would fall into
3 a general category?

4 DR. HIRSCHFELD: Well, that would be a question
5 of the context that one puts it in, and if the angiogenesis
6 inhibitor is one where it's felt it's essential for the
7 tumor maintenance, then I think we would look that way in
8 terms of trying to apply the rule.

9 In terms of other processes, again I would turn
10 the question back to ask for input from the committee
11 because we're again seeking advice. Where should the line
12 be drawn? How focused or how broad should the perception
13 be that the pathway is somehow associated with the
14 tumorigenic state as opposed to general cellular
15 metabolism?

16 DR. SANTANA: But isn't the reality of the
17 situation -- and Rick and you need to help me with this --
18 that companies don't come to you and say --

19 DR. PAZDUR: They're developing it for an
20 indication.

21 DR. SANTANA: Exactly. They're going to come
22 to you and say, I've got this drug that inhibits
23 angiogenesis, and my indication is going to be for the
24 treatment of breast cancer with vascularity of this nature.
25 I'm going to use this drug. How are you going to respond

1 | to that?

2 | DR. PAZDUR: We can only exert authority that
3 | the regulations give us. A product under review must
4 | provide pediatric information if the indication -- and that
5 | depends on what indication they're pursuing -- under review
6 | is a disease found in children. That's the wording. If
7 | the disease is not found in children, a waiver may be
8 | granted.

9 | So, we're kind of extending this by looking at
10 | these pathways, but if a pathway was ubiquitous throughout
11 | all cancers, it would be hard to apply this rule because
12 | you would have to say, well, because of the Pediatric Rule,
13 | all diseases or all drugs that are coming in for cancer now
14 | have to be studied in children. That's one extreme of the
15 | Pediatric Rule. And that's really not the intent of it. I
16 | think we would be challenged very quickly on this, to be
17 | honest with you, if we took a very radical approach to this
18 | by saying, well, this is a common mechanism in all
19 | malignancies. Therefore, all drugs that have this property
20 | must be studied in children. I think there is a specific
21 | connotation here made in the development of the rule in a
22 | sense.

23 | DR. HIRSCHFELD: The other part is the unmet
24 | medical need too. So, if ara C were to come up, then the
25 | question is where would ara C be applied in pediatrics, in

1 | what unmet pediatric medical need. That again would factor
2 | into the decision.

3 | DR. SANTANA: I'd like to make a comment and
4 | try to get back to the last point about the microarray
5 | displays and how they can be utilized. I have to admit to
6 | you publicly that I'm not an expert in this area. I don't
7 | think there are many people in this room that are, except
8 | Todd probably. But my own sense is that it's a new tool
9 | that we don't know enough about. At this point you just
10 | can't assess what its impact is going to be.

11 | So, for the purpose of an academic discussion,
12 | the answer is yes. If you have a new tool that provides
13 | further information that hones down on a specific issue,
14 | then yes, that tool should be used complementary to other
15 | tools that you have. But I don't think we're there yet
16 | with this.

17 | DR. PAZDUR: That I think is an important
18 | point. The way these questions are set up, you're looking
19 | at specific questions, and this is not the clinical
20 | scenario. Obviously, if you have a cytogenetic lesion that
21 | you're looking at, you're also going to have a
22 | histochemistry to look at. You might have immunochemistry.
23 | I think the way we set these questions up was to kind of
24 | purposely bait you, but the real clinical situation is
25 | you're going to have a picture and also the clinical

1 | behavior of the tumor. Does it make sense, given the
2 | biological behavior of a tumor? If it was an indolent
3 | tumor and you found the exact same type of molecular defect
4 | there and the other comparison was a very rapidly growing
5 | tumor, I think a lot of people would take a look back and
6 | say does this really make sense. Again, it's the whole
7 | picture that you're going to look at, not one of these in
8 | isolation.

9 | DR. PARHAM: I have a couple of points about
10 | arrays. I think the real issue is what the question is
11 | you're going to ask with an array experiment. If you're
12 | going to specifically ask whether arrays can be used to
13 | guide therapy, I think there have to be several things set
14 | into protocols.

15 | Number one, protocols should insist on the
16 | maximal amount of tissue necessary to do arrays. We have
17 | to realize that tissue gets divvied up between so many
18 | laboratories now. So, again, I make a plea that we have to
19 | realize that there is strong impetus toward getting less
20 | tissue. So, either arrays will have to use less tissue, or
21 | else we'll have to provide more tissue for entry into
22 | protocols.

23 | The second thing is I think we have to do
24 | careful array experiments to make sure we understand what
25 | happens to tissue between the time it is removed from the

1 | time it is frozen because there is the opportunity for
2 | things like heat shock proteins to be activated and hypoxia
3 | to affect tissues between the time the surgeons take the
4 | tissue out and it sits around on some laboratory shelf
5 | before it's actually frozen. That has to be carefully
6 | controlled.

7 | Then finally, I think it is imperative that we
8 | do confirm array results with other experiments,
9 | particularly immunohistochemistry, not only for
10 | confirmation but for the fact that we may find markers that
11 | we could use immunohistochemistry at a much cheaper cost
12 | and a much wider availability to test.

13 | That was a multiple part thing.

14 | DR. GOLUB: I basically agree with that. It's
15 | too soon to act on any of the small amount of published
16 | work using microarrays in cancer.

17 | I think it is worth getting back to this issue
18 | of the distinction, which I entirely don't understand,
19 | between a specific pathway that's been targeted by a
20 | biological or a new compound and some more general
21 | biological process that may be common to cancer cells and
22 | normal cells. I don't see the fundamental distinction
23 | really at all.

24 | DR. PAZDUR: Do you consider any one of those a
25 | disease? That's going to be the fundamental legal question

1 that's going to be asked if this is brought up before any
2 litigation. Is this a disease recognized by the medical
3 community?

4 DR. GOLUB: Well, I think that's part of what
5 we're talking about. Should we be thinking about cancer as
6 a disease of faulty cell death regulation, adhesion, a
7 disease of faulty cell cycle progression and so on?
8 Probably, but that's much more logical --

9 DR. PAZDUR: And here again, it's the
10 acceptance by the general medical community that these are
11 diseases as such. That's what's going to probably be a
12 legal --

13 DR. SANTANA: I think what you're hearing is
14 that there are some individuals in this room who are
15 beginning to think that way, but I don't think -- and
16 please correct me, the other panel members -- the majority
17 are there yet. I think there are some individuals that are
18 provoking us to think in those ways, but that's not the way
19 it is today.

20 DR. PAZDUR: The point that I was making is we
21 need a scientific basis for that, and I feel that this is
22 evolving at this time.

23 DR. HIRSCHFELD: I would add, just in response
24 to Dr. Golub's query, we've taken one extreme I think
25 intentionally for discussion purposes and we started the

1 | day at another extreme. I think it will be an evolving
2 | process. As we make decisions and engage in consultations,
3 | we'll see where the boundaries begin to shake out.

4 | I'd like other panel members to make comments,
5 | but I would request Dr. Santana as the chair, when he's
6 | ready to conclude the discussion, just to try to summarize.
7 | I just would make a request that you save enough time, if
8 | you could, just to summarize what you think the
9 | recommendations leave or where we should go.

10 | DR. SANTANA: I'll go ahead and do that now
11 | unless any other panel members have comments. Pat?

12 | DR. REYNOLDS: I just have one question since
13 | what we seemed to have focused on in the last little bit
14 | was essentially what you all would confront in trying to
15 | apply this rule if we tried to ask you to do it from the
16 | broadest of perspectives. Understanding that problem from
17 | your viewpoint and understanding that this rule was not a
18 | law passed by Congress, as I understand it, but a
19 | regulation written by FDA in response to a law passed by
20 | Congress, did the Congress use the word "disease"
21 | specifically in their law or was this part of your
22 | regulation?

23 | DR. PAZDUR: I would have to check into that.

24 | DR. REYNOLDS: Anyway, if it was a regulation
25 | at FDA, couldn't the regulation then be developed a little

1 bit more specifically to --

2 DR. PAZDUR: It could be, but with the current
3 recommendations and the way we have applied it to other
4 people and other situations, there has to be consistency in
5 the application of this. Obviously, if we would change it,
6 it would require an internal discussion at the FDA, as well
7 as potential writing of a new guidance, et cetera. I'm not
8 say that it is impossible to do. I'd have to look into it.

9 But the concept of it was that there is a
10 unique disease that has been studied and it is to carry
11 information from an adult disease to a pediatric disease
12 that is similar or the same. That's where we get into the
13 problem, "similar or the same," and that's what we've been
14 discussing here.

15 In other therapeutic areas, it's very easy.
16 Hypertension in adults; hypertension in children.
17 Depression in children; depression in adults. Ulcerative
18 colitis in children; ulcerative colitis in adults. There
19 are not these big discussions here. When we change our
20 wording of things, it doesn't only impact oncology, it also
21 potentially impacts other diseases.

22 Here again, the way it has been intended is
23 that there was a disease, and we would have to ask is this
24 a disease that we're looking at. When you have a specific
25 marker that's specific for the disease, I think we feel a

1 | lot more comfortable, for example, the genetic marker in
2 | CML, but if you talk about a disturbance in protein
3 | synthesis, that's so vague here I think it would be very
4 | difficult to say that. You're almost committing all drugs
5 | for us to exert the pediatric rule on all drugs that come
6 | through, and I think we would have a very hard time
7 | justifying that.

8 | DR. HIRSCHFELD: I'd like to just add to that
9 | as one of the co-authors of this regulation. In other
10 | situations, as Dr. Pazdur pointed out, it's a metabolic
11 | process. Hypertension. It's something that's occurring in
12 | the vasculature. Or depression. Again, I don't think even
13 | Dr. Burger could, on a brain biopsy, tell us which patient
14 | was depressed and which was not. These are processes going
15 | on.

16 | One of the hopes I always had in helping craft
17 | this was that we could move oncology from an histology
18 | based paradigm to thinking of it in terms of a process, as
19 | we do hypertension and depression. That's obviously a
20 | challenge and that's one of the reasons we asked all of you
21 | to come and help us sort this out. That's where our
22 | thinking, at least, was originating from. I don't know if
23 | that answers your question, Dr. Reynolds.

24 | DR. REYNOLDS: Well, it does. Again, it's not
25 | so much a question but more a suggestion that maybe the

1 solution to this dilemma that we're facing here would be to
2 consider adding some language to the regulation dealing
3 with the field of oncology that would not box you in or
4 cause undue heartache to the pharmaceutical industry, but
5 would allow a little bit more liberal application of this
6 rule to encourage more agents into pediatrics.

7 DR. SANTANA: If I could then summarize so that
8 we can adjourn. We really only covered question number 1.
9 My feeling from the discussion is that the diagnostic
10 criteria that are used are complementary to each other,
11 that there will be certain scenarios where one is
12 sufficient but, as we all come to recognize, the more
13 information you have and the more you complement these, the
14 better you are in terms of linking them as a group or
15 linking them to similarities that may occur in adults.

16 I think the other thing you've heard is that
17 there may be specific examples in which there are genetic
18 or antigenic or whatever lesions that are so specific in
19 the pathogenesis and the impact that those compounds would
20 have on those, that those would be specific enough in a
21 sense, but also broad enough in terms of how they relate to
22 adults, that you could consider those separately. I think
23 that's what the group was saying.

24 DR. HIRSCHFELD: We thank you for your advice
25 and input on this.

1 DR. SANTANA: It's been a very challenging
2 afternoon. I want to thank all the panel members and all
3 the audience for their participation. Thank you.

4 (Whereupon, at 5:08 p.m., the subcommittee was
5 adjourned.)
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