dose-response curve we're looking at.

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

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

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

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

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

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

Comment?

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

One of the few is a randomized study that was

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

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

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

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

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

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

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

(Laughter.)

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

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

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

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

just not going to happen.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

applicable to both types.

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

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

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

(Recess.)

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

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

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

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

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

Mr. Chairman.

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

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

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

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

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

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

Susan.

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

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

DR. SANTANA: David?

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

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

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

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

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

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

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

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

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

DR. SANTANA: Any other further comments? Frank?

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

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

DR. SANTANA: Jim?

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

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

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

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

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

DR. SANTANA: But I think the critical

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

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

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

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

David.

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

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

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

Todd.

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

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

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

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

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

DR. REYNOLDS: But looks a little and behaves a

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

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

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

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

DR. SANTANA: Sue.

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

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

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

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

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

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

DR. COHN: Yes.

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

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

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

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

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

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

DR. PARHAM: Right, and particularly the rare ones.

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

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

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

DR. SANTANA: Peter?

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

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

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

DR. BURGER: Yes, right.

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

DR. SANTANA: Steve.

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

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

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

DR. SANTANA: Jim?

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

DR. SANTANA: A point well taken.

Any further discussion?

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

DR. SANTANA: Peter?

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

DR. SANTANA: Frank?

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

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

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

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

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

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

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

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

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

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

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

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

But as I said, I just think each one of these, as an individual lesion, you need to consider very carefully because it depends upon sort of like the cytogenetic lesion. If the cytogenetic lesion is truly what is involved in the pathogenesis of the tumor and your drug is specific for that cytogenetic lesion, then it all makes a lot of sense. If it is not central to the pathogenesis of the tumor, but rather just associated because there's more rapid proliferation associated with certain oncogene expressions or 1p deletions, but it's not central to pathogenesis, then I think that that's a totally separate issue.

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

in making your decisions.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

in the pediatric patients.

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

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

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

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

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

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

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

DR. REYNOLDS: Well, getting the agents in the

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

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

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

DR. SANTANA: Well, the science would trigger

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

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

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

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

DR. SANTANA: Does anybody want to address that?

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

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

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

DR. SANTANA: I think the consensus is yes.

Donna?

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

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

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

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

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

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

(Laughter.)

DR. HIRSCHFELD: And a lot more mice too.

DR. SANTANA: Malcolm?

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

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

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

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

medical need.

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

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

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

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

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

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

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

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

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

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

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

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

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

target it.

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

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

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

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

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

Another one I want to throw in is for

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Todd, do you want to address that?

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

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

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

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

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

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

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

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

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

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

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

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

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

to that?

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

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

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

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

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

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

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

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

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

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

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

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

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

That was a multiple part thing.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

bit more specifically to --

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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