

1 extraskkeletal myxoid chondrosarcoma which is a
2 disease of adults.

3 So, some of the sarcomas do have specific
4 translocations that are identified. The vast
5 majority do not. A lot of the translocations
6 involve the EWS gene but there is a huge difference
7 between those which are in the Ewing's PNET group,
8 which are very sensitive to chemotherapy, and some
9 of the others such as desmoplastic small round cell
10 tumor which is a disaster and even some of the
11 myxoid liposarcomas which have an EWS
12 translocation, or extraskkeletal myxoid
13 chondrosarcoma which is very resistant. So, the
14 presence of EWS as part of the translocation
15 doesn't mean that you are going to have the
16 sensitivity that we see in Ewing's sarcoma.

17 [Slide]

18 I was once asked what is the best regimen
19 for adult soft tissue sarcomas? And, the answer is
20 it depends on which sarcoma and which patient, but
21 we haven't done the studies to prove that. So, let
22 me show you the reasons why I think this is
23 important and I think the reasons why we got
24 confused.

25 [Slide]

1 When sarcoma chemotherapy started in
2 adults about 30 years ago, it started with a drug
3 called Adriamycin before it was called doxorubicin.
4 The response rates, which may be different in the
5 way they were done to the way they are done now,
6 are more or less the same across histologies. The
7 only exception, and it is not a soft tissue
8 sarcoma, was chondrosarcoma where the response rate
9 was lower. But if you look, for example, at
10 leiomyosarcoma, one of the common groups, and
11 synovial sarcoma, another one of the common
12 histologies -- more or less the same response. So,
13 I think we got into the mind set that sarcomas are
14 all the same and they all respond the same way to
15 chemotherapy.

16 [Slide]

17 Well, there aren't very many good drugs
18 for the treatment of sarcomas. This is one where
19 DTIC was added to Adriamycin and again you saw the
20 same sort of breakdown more or less by histologic
21 group, and there wasn't a big difference.

22 [Slide]

23 There was a big difference by primary
24 site. This was pointed out in 1975 by Jeff Gotlieb
25 who said that tumors that arose in the GI tract,

1 even though they were primarily called
2 leiomyosarcomas, had a much lower rate of response
3 than tumors that arose in the GU tract, even though
4 most of those were called leiomyosarcomas. He
5 suggested that there was some biologic difference.

6 [Slide]

7 But if you look at synovial sarcoma, now
8 with ifosfamide, the other real drug for adult soft
9 tissue sarcomas, in a number of studies -- this is
10 our data, combined second-, third-, fourth-line
11 therapy for synovial sarcoma, a higher response, 31
12 percent versus an average of about 20; and,
13 leiomyosarcomas, whether of GI or other origin,
14 only about 10 percent. Well, you know, that may be
15 just per chance so let's look at some other
16 studies.

17 [Slide]

18 Karen Antman's study, synovial sarcoma, 40
19 percent; leiomyosarcoma, 7 percent. Here,
20 reasonable numbers of patients, 27 patients with
21 leiomyosarcomas. So, you have to think that maybe
22 ifosfamide is not a particularly good drug for
23 leiomyosarcoma.

24 [Slide]

25 Here is Le Cesne's high dose ifosfamide

1 study, 11 patients with leiomyosarcoma and no
2 response; 4 with synovial sarcoma, 3 responses.
3 Again, small numbers but everyone doing the same
4 thing. Synovial sarcoma is more responsive to
5 ifosfamide and leiomyosarcoma is less responsive to
6 ifosfamide.

7 So, if you then look at combination
8 studies, and I am not going to get into a whole lot
9 of them but if you are looking at
10 Adriamycin-ifosfamide and you simply report the
11 data out as sarcomas, it is uninterpretable data.
12 You need to know what you have of what in that mix.

13 [Slide]

14 So, what we have used primarily at
15 Anderson over the past several years as a
16 front-line therapy is Adriamycin and ifosfamide
17 with attempts to maximize dose because these tumors
18 have very steep dose responses. Mike Link's
19 comment about whether a pediatric oncologist or
20 medical oncologist treats you is right on. The
21 pediatric oncologists give more intensive
22 chemotherapy. The medical oncologists are babies;
23 they don't like to make people sick. They don't
24 like to get calls in the middle of the night. So,
25 they don't treat their solid tumor patients as if

1 they had acute leukemia, except for those who just
2 do sarcomas who look and see, "well, wait a minute,
3 if you want to get a result you have to give those
4 high doses so you have to make them sick." And, we
5 are a lot more like the pediatricians.

6 [Slide]

7 That is supposed to be a "less than or
8 equal to" sign, 65. We have no exclusions for
9 children on our studies. As a matter of fact, our
10 front-line studies for osteosarcoma and Ewing's
11 sarcoma are joint studies between pediatrics and
12 sarcoma medical oncology. There is no difference.
13 We treat them the same. They are the same
14 diseases. The adults do worse; the pediatric
15 patients do better. They tolerate therapy better.
16 But we can give it. You can't give 75/10 to a
17 65-plus year old adult because even though they
18 appear totally normal, they have abnormal kidney
19 function because kidneys age, and what we found out
20 the hard way is that if you really push these
21 people it is very easy to cause renal failure. So,
22 we look for renal function. We look at questions
23 of whether or not patients have two kidneys because
24 a lot of people with retroperitoneal sarcomas have
25 had a kidney removed. So, for those people, even

1 though their renal function is supposedly adequate,
2 it is not adequate when you give them high dose
3 ifosfamide. So, we have to be worried about that
4 sort of issue in dealing with sarcomas.

5 But when we started our treatments and all
6 of our protocols for dose-intensive
7 Adriamycin-ifosfamide we excluded people with
8 gastrointestinal leiomyosarcoma. That was the
9 diagnosis at that time. We excluded alveolar soft
10 part sarcoma because it doesn't respond to either
11 Adriamycin or ifosfamide in the small number of
12 patients that have been treated. And, we excluded
13 clear cell sarcoma because it doesn't respond very
14 well.

15 [Slide]

16 Overall, we have a response rate of about
17 60-something percent in this group of patients, but
18 there is a difference based on histology, and that
19 is the point that I was going to get at. With both
20 Adriamycin and ifosfamide you would expect that
21 synovial sarcoma, the most ifosfamide sensitive,
22 would do the best.

23 [Slide]

24 In fact, it does. We get an 88 percent
25 response rate. Angiosarcomas are very sensitive to

1 both drugs. Unfortunately, they also recur very
2 rapidly. I will get back to angiosarcomas a little
3 bit later. Malignant fibrocystoma, which is
4 probably five or six different diseases
5 characterized by pleomorphic histology and large
6 cells, responds well. There may be differences
7 within the subgroups but they all tend to respond.

8 But even the non-GI leiomyosarcomas that
9 we put on this study have only a 50 percent
10 response rate. So, there is a difference based on
11 what kind of sarcoma you have, and none of the
12 studies in adults have addressed this. Can you
13 imagine if we tried to now do disease-specific
14 studies in pediatric patients with these
15 histologies? That is impossible. We are just
16 getting to the point where maybe we can do an adult
17 study in a specific histology. If we add on the
18 pediatric patients, we can add them into the
19 disease-specific studies but you could never do a
20 study. It would take you 50 years to do the study,
21 by which time they wouldn't be pediatric patients
22 anymore.

23 [Laughter]

24 [Slide]

25 So, I think we need to get into

1 disease-specific therapy and the hints of this are
2 just now coming.

3 [Slide]

4 As we move into the new future where we
5 are getting into genetically specific molecular
6 therapy -- this is a slide that John Edmonston made
7 up about ten years ago and I liked it because that
8 was the time when we were the dinosaurs. I mean,
9 you know, we are going to think back on this era 50
10 years from now and say we were barbarians.

11 But the patients are here, and they are
12 dying, and we have to treat them now. But we now
13 have the first hint that the genetically specific
14 molecular therapy will, in fact, work and that is
15 in GI stromal tumors. These are the things we used
16 to call GI leiomyosarcomas. As I said, 25 years
17 ago Jeff Gotlieb said they are different; they
18 don't respond to therapy the same way.

19 [Slide]

20 About five years ago the pathologists
21 started recognizing that they were different and
22 gave them a different name and called them GI
23 stromal tumors and the key to these tumors is that
24 they come from the interstitial cell of Cahal which
25 constitutively expresses c-Kit, and about 90

1 percent of those tumors which you would call GIST
2 based on light microscopy are c-Kit positive.

3 It happens that c-Kit is inhibited by
4 Gleevec and the preliminary data that were
5 presented at plenary session at ASCO were very
6 exciting. So, an intergroup study started and
7 every sarcoma investigator in the world is
8 participating either in the U.S. or the European
9 version of this intergroup study. So, in the past
10 six months we have entered probably more than 70
11 patients with GI stromal tumors because we had them
12 waiting in the wings. We had been keeping them
13 alive by doing surgery or by doing chemo
14 embolizations of their liver, and they are coming
15 out of the woodwork.

16 Preliminary data from our group of
17 patients -- if you use traditional criteria for
18 response at 8 weeks, there is about a 30 percent
19 response rate or 40 percent response rate. If you
20 use PET scanning, it is a 70 percent response rate.
21 I think if we continue to follow we are going to
22 see the higher response because that is what was
23 shown in the earlier studies. But that also raises
24 the question that I will get back to, that we don't
25 know how to measure response.

1 [Slide]

2 Let me just go over to a couple of other
3 specific tumors, myxoid liposarcomas, again a
4 specific translocation different from other
5 liposarcomas. So, this is a specific disease
6 within the liposarcoma family. It is the only one
7 where differentiation therapy with either
8 PPAR-gamma or retinoid-X receptor agonists seems to
9 be effective. So, again, a specific target for a
10 specific therapy.

11 [Slide]

12 Angiosarcomas, a group of very difficult
13 tumors because they respond well but they relapse
14 rapidly and often they occur in elderly people on
15 the scalp. These people can't tolerate the same
16 kind of aggressive chemotherapy that we give to the
17 younger people. Taxol, in a series from Memorial
18 that is not even a formal study -- responses in 8/9
19 patients. Taxol doesn't work in sarcomas. The
20 Memorial study which had 2/28, one of which was an
21 angiosarcoma -- it is 1/27 in the other
22 histologies. We did Taxol in 19 patients, no
23 angiosarcomas, no responses. Taxol is not a
24 sarcoma drug but it works for angiosarcoma. It is
25 a different disease.

1 We haven't done a formal study but we have
2 treated patients with Taxol and the people at
3 Memorial are right, it really works. So, this is a
4 therapy that can be given. Weekly Taxol is easy
5 for a 70-year old. It can be given. It can even
6 be given by the local medical oncologist because
7 they know how to do Taxol.

8 Epithelioid hemangioendothelioma -- a
9 weird disease; doesn't occur in children, I don't
10 think. I haven't seen one. Primary tumors in
11 liver, they have been treated with liver
12 transplantation. They also can undergo spontaneous
13 remission. But if you have a lesion that is
14 growing, embolization, cutting off the vasculature,
15 is very effective. Interferon is very effective.
16 The new angiogenesis inhibitors haven't been
17 studied -- beautiful target.

18 [Slide]

19 I can't show you the slide I wanted to
20 show you unless I take my Mac up and hook it up to
21 this, but our definitions of response are all based
22 on tumor shrinkage and sarcomas clearly do not
23 always shrink when they die and we miss a huge
24 amount by not using more sophisticated methodology
25 to assess the effectiveness of our drugs.

1 One of the things that can happen, which
2 this slide would show if you have enough
3 imagination, is a tumor in the mediastinum that
4 grew in size a little bit but became totally
5 necrotic on CT. We looked at it and we said this
6 is a great response. I have shown that slide to
7 groups of people around the country at various
8 places and I said what would you call it? And, 90
9 percent of medical oncologists would call it stable
10 or progressive disease. There are only a few that
11 will call it a response. Well, when you have
12 progressive metastatic disease, usually it is time
13 to give up and send the patient to hospice. We had
14 our thoracic surgeons go in, take out the tumor
15 along with aorta because that was what was
16 required, and the patient is alive and well five
17 years later. Less than one percent viable tumor in
18 the specimen.

19 We learned in osteosarcoma that if the
20 tumor is dead it is a good prognosis. It means the
21 therapy worked. We have to figure out ways of
22 measuring, short of surgery, when tumors are dead.
23 And, at least a hint from the GIST experiment is
24 that PET scanning is maybe a way to do that but
25 other techniques -- dynamic MRI, dynamic CT and

1 probably other things that I haven't even dreamed
2 of are an approach but we have to get out of the
3 box and think about shrinkage because we are going
4 to miss drugs that are active.

5 [Slide]

6 So, I think we need to start looking at
7 other approaches and that is important.

8 [Slide]

9 So, getting back to pediatrics, where does
10 all of this fit in? In the adult sarcoma community
11 we are moving more and more towards accepting that
12 these many tumors are very different, that we
13 really do need to do studies where we address each
14 of the different groups and then follow-up on leads
15 on the groups that are positive. As we get
16 molecular markers of these groups, we will move
17 into molecular markers as ways of going. But they
18 are not all the same. We are going to have to get
19 separate trials, and I would include children with
20 the specific diseases on these trials. To try to
21 do a separate disease in children I think would be
22 fruitless. Thank you.

23 DR. SANTANA: Thank you, Bob. We have
24 other individuals in the committee with expertise
25 in this area so I would invite Paul, Anthony and

1 others with expertise in this particular area of
2 discussion to make comments now.

3 Discussion

4 DR. MEYERS: I would like to make several
5 comments. I think the point that Bob is making
6 about thinking of novel ways to evaluate tumor
7 response is extraordinarily important. Not only is
8 the technology that we use important, but the
9 timing. Dr. Elias was heavily involved in the
10 development of a drug, ET743, where we learned that
11 if we had used the conventional time point to
12 evaluate that drug we would probably have discarded
13 it early on, and the patients with soft tissue
14 sarcomas continue to respond in a manner very
15 different from our conventional use of cytotoxic
16 chemotherapy. You can see a very modest response
17 after one or two cycles, and if you continue the
18 drug for three, four, five, six, seven cycles you
19 continue to see responses and sometimes ultimately
20 achieve the conventional definition of a partial or
21 complete response for these patients. We need to
22 be sure that we don't discard some of these novel
23 compounds, which may be working by different
24 mechanisms from conventional cytotoxic
25 chemotherapy, by using too early a time point and

1 discarding a drug that may still have activity.

2 Again, I would concur very much with what
3 Bob said, that I have not seen any convincing
4 evidence -- just as Henry did looking at the brain
5 tumors, I have not seen any convincing evidence
6 that these sarcomas, when carefully defined,
7 ideally defined by a consistent chromosomal
8 translocation, behave any differently in children
9 from adults. I think that our decisions about
10 therapies and which therapies to employ and which
11 new agents to bring forward into clinical trial
12 should be based on the biology of the tumors
13 whenever possible.

14 I do need to comment, however, just
15 briefly because in our first session this morning
16 we heard I think some very encouraging comments
17 that we were going to use the efficacy to drive the
18 process much, much more than toxicity, and handle
19 toxicity perhaps appropriately through labeling,
20 and point out that I had an opportunity -- and this
21 is a trial that Dr. Benjamin is also involved in --
22 to attend a meeting of the Recombinant DNA Advisory
23 Committee just two weeks ago. We have proposed a
24 trial for a gene therapy approach for metastatic
25 recurrent osteosarcoma, and the RAC was unwilling

1 to accept what we just discussed here today, that
2 the trial should be open to patients with
3 metastatic recurrent osteosarcoma regardless of
4 age. They felt that that approach could not be
5 offered to patients under the age of 18 until the
6 safety of the approach had been established in
7 patients greater than 18. So, the consensus that I
8 am getting from many of the individuals around this
9 table is not universally shared in the regulatory
10 community.

11 DR. SANTANA: Dr. Elias, do you want to
12 make any comments?

13 DR. ELIAS: Well, I would like to also
14 agree with what Dr. Benjamin has said. I mean, it
15 is quite clear that the individual histologies have
16 enormous differences in terms of response to the
17 conventional chemotherapy agents, and that has been
18 known for years, but the real difficulty has been
19 that no one institution and even groups of
20 institutions have sufficient numbers.

21 I think it is extraordinarily heartening
22 to see the amazing productivity of the GIST trials,
23 and the ability to mobilize a whole community
24 worldwide to actually target this. I think one of
25 the issues with sarcomas is, because they have a

1 more simplified genome or alteration in genome
2 relative, for example, to common epithelial tumors,
3 they can represent a situation of proof of
4 principle so that you have a more discrete pathway,
5 lesion, etc., what-have-you so that at least from
6 the pharmaceutical standpoint you could, in fact,
7 justify developing the drugs in these diseases.

8 DR. SANTANA: David?

9 DR. PARHAM: I agree that histology is a
10 very key thing in sarcomas, but I think it is also
11 equally important to take in the effects of grade
12 because within the confines of grade a low grade
13 sarcoma will do relatively the same if it is
14 localized, whether it is a synovial sarcoma or a
15 peripheral nerve sheath tumor or fibrosarcoma. So,
16 I think that would be a key thing to keep in mind
17 when we talk about treating things according to
18 histology. The histology may not be as important
19 as grade.

20 DR. SANTANA: Do you want to make a
21 comment, David?

22 DR. POPLACK: Yes, I am a little perplexed
23 by the comment that you made, Paul, regarding the
24 unwillingness to accept the similarity of a tumor
25 between adults and pediatrics. I think the issue

1 that you were speaking of with the RAC is a safety
2 issue, and that is not being necessarily addressed
3 in these discussions. Is that not the case?

4 DR. HIRSCHFELD: I would concur with Dr.
5 Poplack that the safety issues are not the topic,
6 but I think I will let Dr. Meyers answer but I
7 think he was just raising an axillary point.

8 DR. MEYERS: I think it is inseparable,
9 and this is the question that I was placing to
10 Henry. As we prioritize, moving forward with novel
11 agents, it will be both an issue of what agents
12 give us the greatest potential for benefit and what
13 is the risk/benefit ratio that we perceive for one
14 of these agents. I was encouraged to hear that we
15 were placing a strong emphasis on the first half of
16 that balance. I think that the emphasis was
17 perhaps over-weighted in terms of the risk side of
18 that equation at the hearing that I attended.

19 DR. SANTANA: I don't want to get into a
20 public discussion of this auxiliary issue because I
21 think the points have been made. I just think we
22 have to be sensitive that there are environmental
23 issues of current things that are happening in that
24 regard that I am sure influence a lot of these
25 discussions in other committees. Malcolm?

1 DR. SMITH: Several speakers have
2 addressed the issue of studying these tumors that
3 cross the pediatric-adult line together and the
4 benefits of doing that. There is a paradigm for
5 doing that, and that is the leukemia world with
6 acute promyelocytic leukemia. Since the early
7 1990's, the first intergroup trial for APL that
8 studied all transretinoic acid was amended to
9 include pediatric patients, and the then Pediatric
10 Oncology Group and the Children's Cancer Group
11 participated in that adult cooperative group-led
12 trial.

13 The current APL trial is examining arsenic
14 trioxide and one of the randomizations is
15 plus/minus arsenic trioxide. When that trial began
16 there wasn't much data concerning the safety of
17 arsenic trioxide in children, but those data have
18 emerged since the trial was initiated and the trial
19 is being amended so that children over five years
20 of age will be able to participate in the arsenic
21 trioxide trial randomization. So, there is a
22 paradigm for when there is a similarity at the
23 molecular level between the pediatric and the adult
24 condition, how those can be studied together
25 appropriately in the same clinical trial.

1 Maybe Paul and others can comment on this,
2 but CTAP has really been encouraging the bone
3 sarcoma and the soft tissue sarcoma committees and
4 COG and then the adult cooperative groups to work
5 together to study these cancers as they do cross
6 the adult-pediatric age distinction. That is an
7 artificial barrier and a number of efforts are
8 being made to try to stimulate such collaborative
9 research.

10 DR. SANTANA: I think those comments are
11 important. I think there has been a merging of the
12 consensus that at least when it relates to sarcomas
13 in adults and children there may be more
14 similarities since, at least in pediatrics, a good
15 portion of these patients are cured. And, the
16 challenge of the number of patients can only be
17 dealt with by a collaborative effort between adults
18 and pediatric studies. At least from my
19 perspective, I think that is the way to move in
20 this particular disease category. Any other
21 comments before we get to the questions?

22 [No response]

23 We have a series of questions that we have
24 to answer or give advice to the FDA on -- yes, we
25 may continue the discussion if somebody has another

1 question. Go ahead, Donna.

2 DR. PRZEPIORKA: Two questions for Dr.
3 Link. I enjoyed the slide, the ten-year old slide
4 that Dr. Benjamin showed about the dinosaur age,
5 and him mentioning that, you know, we still have
6 patients and although we like molecular therapy we
7 are still kind of in the dinosaur age. So, my
8 first question to you is how do you choose drugs
9 for your patients nowadays? When you have somebody
10 with recurrent disease and you have to treat them,
11 on what basis do you choose drugs to develop?

12 DR. LINK: In the recurrent situation -- I
13 think that would also apply to patients who have
14 very high risk disease. So, we view those as
15 similar categories, patients who are candidates for
16 more experimental therapies. Most of us I think
17 would participate in -- because, again, the
18 Pediatric Cooperative Group is such an
19 all-encompassing thing and most of our patients are
20 on clinical trials -- the majority of patients --
21 well, I should back up, many patients who develop
22 recurrent disease have become candidates for Phase
23 II or Phase I trials that are usually
24 CTAP-sponsored trials so that they are entered on
25 those trials.

1 Now, one of the problems, particularly
2 with rhabdomyosarcoma, is that there are a lot of
3 active agents that have not proven useful when
4 added to the standard combination. It is an irony
5 which is unfortunate. So, the standard combination
6 which we use today, although it has been tweaked
7 many times, is the same combination of drugs that
8 has been available since the 1970's. I was a
9 fellow when we were using the same therapy.

10 Since then many drugs have come along
11 which show obvious activity, and many pediatric
12 oncologists feel that in a patient who develops
13 recurrence you sort of have to go through what is
14 available as treatment before you sort of begin to
15 use an investigational agent. I mean, I think that
16 is a philosophical problem rather than anything
17 else. Many of us would try a Phase I trial and
18 then put them on a standard agent. So, there are
19 some problems there.

20 In most of the other diseases, like
21 refractory Ewing's sarcoma or osteosarcoma, I think
22 that those patients are candidates for either a
23 biological or whatever experimental agent, mostly
24 in the context of a clinical trial.

25 DR. PRZEPIORKA: There is nothing specific

1 about the disease, however, that points you towards
2 one set of drugs versus another set of drugs
3 empirically?

4 DR. LINK: Well, there are now. For
5 example, the rationale for Gleevec is leading to
6 the initiation of a trial to study those patients.
7 So, for example, the results in GIST tumors, a very
8 refractory tumor that responds to this -- I suspect
9 that many patients will end up on a trial like
10 that. But I don't know how one would pick and
11 choose otherwise, except for the fact that they
12 have been prioritized one way or the other, either
13 just because it is the standard Phase II drug that
14 is being studied and that is the next candidate on
15 the list, or sometimes when there is a particular
16 drug of interest which is being prioritized by a
17 specific disease committee, they want to try that
18 but we often will have a specific retrieval
19 protocol mandated and that would be the next trial
20 that the patient would be eligible for.

21 DR. PRZEPIORKA: You mentioned a number of
22 new translocations that are very useful for
23 diagnostic purposes in the pediatric sarcomas,
24 especially in the Ewing's family, and the questions
25 I have for you are, are the functions of the fusion

1 transcripts known? If so, what are they? And,
2 secondly, you also mentioned a number of biologic
3 correlations, such as PGF and Her2 expression, but
4 I didn't hear anything about any preclinical data
5 that would suggest that inhibition of those
6 receptors actually has any function in inhibition
7 of growth of the pediatric sarcomas.

8 DR. LINK: I will address the second
9 question first because I have to think about what
10 your first question was. The mutated c-Kit
11 expression in Ewing's sarcoma and in Ewing's lines
12 has been shown in vitro. You can get abrogation of
13 cell growth, or whatever the appropriate endpoint
14 would be in vitro. So, there is something more
15 than just that it has the c-Kit and so we should
16 target it because it worked in GIST. I mean, there
17 is more data than that. I am not party to all of
18 it, but it is available. So, some of that
19 preclinical stuff has been done but not in all
20 tumors.

21 Her2 was your specific question? What was
22 it?

23 DR. PRZEPIORKA: The function of the
24 transcripts in the Ewing's family?

25 DR. LINK: Oh, I mean some of them are

1 known and they are clearly downstream. These are
2 transcription factors so that there is clearly a
3 whole myriad of downstream genes which are turned
4 down by these. Some of it is fairly well
5 characterized, but I think we don't know the whole
6 gamut of what the consequence of the translocation
7 is. Other people may want to comment on that but
8 some of it is known but I think the entirety of
9 what the consequence is unknown.

10 DR. SANTANA: There is great effort also
11 in creating some knockout models of some of these
12 transcripts and looking at what the phenotype is in
13 animals if you do those kind of experiments. I am
14 aware of some work in rhabdomyosarcoma in that
15 regard.

16 DR. POMEROY: Some of the transcription
17 factors are very difficult targets for soluble
18 small molecules. I think the value of tyrosine
19 kinase inhibitors is that these molecules are
20 relatively accessible on the cell surface, and
21 things that work within the nucleus are much more
22 difficult to target. So, although we can
23 understand in some cases specific biological
24 mechanisms of how tumors grow, they won't all be
25 equal in terms of how they might be attacked.

1 DR. KUN: Just one slightly related
2 question, in the case of APL it is not difficult in
3 adult oncology to get pathologists to send those
4 samples off for molecular diagnostics. My
5 experience has been in a number of hospitals for
6 adult sarcomas which are not that common but we see
7 them enough, pathologists are very reluctant. It
8 seems that they feel the gold standard still is
9 their histology or histopathology so when they call
10 it alveolar, embryonal or synovial sarcoma that is
11 sufficient, and we often don't get au courant
12 molecular diagnostics on these patients and we are
13 missing out on a lot of information I think that
14 leads to this.

15 So, one recommendation might be just to
16 stress the importance of these molecular
17 diagnostics, which will be essential in this time
18 where there are clearly adult and pediatric links.
19 But there is a lot of information that is not being
20 gotten because pathologists -- certainly off
21 clinical trials, which most of them in the adult
22 world still are, aren't getting this information.

23 DR. SANTANA: David, do you want to
24 follow-up on that?

25 DR. PARHAM: Right. First, I would like

1 to address one question, that is, there are at
2 least 20 upstream and downstream modulators of that
3 fusion gene that you just asked about. There is a
4 cottage industry of literature appearing on that.

5 But as to the question of diagnosis, this
6 is becoming a greater question with each passing
7 year because pathologists are becoming more and
8 more efficient at arriving at a histologic
9 diagnosis using fine-needle aspiration biopsy and
10 similar things which have much less morbidity for a
11 patient. So, if the criteria for putting a patient
12 on study is simply histologic diagnosis, we are
13 going to be in a situation where we are getting
14 less tissue, not more. I don't think pathologists
15 have any problem with sending tissue off, but there
16 always is that question of how much is adequate.

17 There have been some recent things coming
18 out from CIOP. I think it is going to be in the
19 upcoming Ped. Onco., about how to handle
20 fine-needle aspirations for biologic studies. But
21 the point is pathologists are willing to send it
22 out, but it is always a question of how much do you
23 get and this is an issue that is going to have to
24 be addressed if we want to do biologic studies.

25 DR. SANTANA: I know from other

1 conversations with investigators that I have had
2 that the COG has had a major recent effort in their
3 sarcoma working group, and Mike may want to
4 comment, specifically looking at this issue in a
5 subcategory of patients with soft tissue sarcoma to
6 establish a biology type protocol to try to resolve
7 this issue. So, it is done in a group-wide effort
8 because we just don't know -- people don't know
9 where to send the samples; they don't know who to
10 contact. So, they are trying to do it in a
11 collaborative effort. So, I know that at least in
12 the pediatric community there is a major effort
13 being placed on this particular question in the
14 soft tissue sarcoma field.

15 DR. LINK: I would just make the comment
16 that the answer to your question is you have to
17 start doing things the way pediatrics do it.

18 [Laughter]

19 Because basically what you do, first of
20 all, you get a monopoly on the market. So, all the
21 kids are seen in places where they are all put on
22 clinical trials. The clinical trial becomes the
23 standard of care. Then you up the ante and say you
24 want the kid to go on a clinical trial; you have to
25 get the tissue or the kid is not eligible for the

1 trial; or you have to get a letter from your mother
2 or something like that which says why you didn't
3 get the tissue. That is how we do it. That is why
4 if you look at kids with a variety of solid tumors
5 -- neuroblastoma, Ewing's sarcoma -- we are now
6 recapitulating what went on in lymphoblastic
7 leukemia where, admittedly, it is much easier to
8 get the stuff. But we wouldn't let a patient on a
9 trial unless you got the cytogenetics and got all
10 the stuff that you need to risk stratify the
11 patient.

12 That is happening in neuroblastoma now.
13 We don't even know how to treat -- this is now
14 standard of care. I mean, Sue could comment on it
15 better than I, that we don't even know how to treat
16 a kid with neuroblastoma unless you do the biologic
17 studies because that determines the outcome. So,
18 that is an editorial pitch but maybe that is the
19 answer.

20 DR. COHN: Yes, I was just going to say in
21 terms of neuroblastoma, I mean the advantage that
22 we have in neuroblastoma is we define the therapy
23 according to the molecular genetics. We don't care
24 about their stage and age anymore. Now, in this
25 new biology study we are going to be obtaining 1P,

1 11Q, 17Q, 14Q. So we have hopefully the whole
2 gamut covered. But the difference is that you need
3 the information to determine the therapy. So,
4 there is the carrot and the stick. You can't
5 decide how to treat this patient without knowing
6 all the genetic abnormalities.

7 DR. LEVIN: What happens if you have all
8 the genetic abnormalities and the therapy that you
9 envision is something that requires two
10 experimental drugs from two companies? To give you
11 a good example, osteosarcoma -- it looks like what
12 you should do is you should take a PDGF receptor
13 inhibitor like STI -- Gleevec, and you should take
14 a pan SARK RTK inhibitor, which would get the
15 receptor as well. So, maybe that is what you
16 should do. So, the question is how can you
17 expedite that kind of a process and move it
18 forward? But that would be based on genetic
19 information; that would be based on signaling logic
20 and it is testable. It is more valuable probably
21 than testing one of those receptors.

22 DR. HIRSCHFELD: I think excellent
23 diplomatic skills is going to be the way to solve
24 that one.

25 [Laughter]

1 DR. ELIAS: Just one comment. I was
2 intrigued in terms of the discussion of what do you
3 do for recurrent Ewing's? Namely, you take the
4 drugs that previously showed activity. I think we
5 are getting into that problem in adult medicine. I
6 mean, in breast cancer we have drugs that are
7 developed and approved for second-line, for
8 third-line. We are working on fourth-line.

9 Ultimately, while that is a very good
10 strategy for the pharmaceutical companies and for
11 the drugs to develop a niche to get approved, what
12 it does also do is mean that in a sense there is
13 some mandate to require that a patient, before they
14 get to an experimental agent, has had their first,
15 second, third, fourth, whatever. And, this is an
16 increasing problem, and I think there is not data
17 that one has to use a particular sequence. On the
18 other hand, this is what is being used, such that
19 only two percent or so of adults actually go on
20 clinical trial, and I think that is even going to
21 get worse as we get into this fixed sequence of
22 trials based on what is FDA recommended and,
23 therefore, what the insurance companies are going
24 to pay for.

25 DR. HIRSCHFELD: I just want to clarify,

1 we don't recommend or endorse trials particularly.
2 We allow them to proceed on the basis of safety
3 evaluation.

4 DR. ELIAS: I am sorry, I am not
5 disagreeing with that but, you know, they are
6 approved for second- or third-line use. In other
7 words, they have developed a specific niche so that
8 taxotere is approved for second-line use in
9 non-small cell lung cancer or breast cancer, and so
10 forth. NTA, I believe, is being developed for
11 fourth-line Zeloda refractory patients because
12 Zeloda is now approved for third-line. So, we are
13 getting an increasing, sort of regimented, set of
14 treatments and these are the approved indications
15 and the insurance companies are not paying for
16 anything that isn't approved in a sense. So, there
17 is a difficulty there.

18 DR. PAZDUR: This is a manifestation of
19 accelerated approval. Okay? And, this is a game
20 that many of the drug companies that come in play
21 with us to define what is an unmet medical need in
22 order to get their drug approved on basically the
23 least amount of information possible and the
24 smallest population, and to try to get a more and
25 more refractory patient population. For example,

1 if we approve at ODAC a drug in third-line breast
2 cancer or something with a 10 percent response
3 rate, the following week we have an army of people
4 coming in wanting to know what is the minimum
5 response rate it will take and the smallest number
6 of patients and in the most refractory population.

7 We are trying to discourage this strongly,
8 believe me. It doesn't serve anybody any good in a
9 situation -- yes, it could get a drug approved but
10 as far as moving the science forward I really
11 question it. It may not even be doing the drug any
12 good because as you study drugs in more refractory
13 populations the chances of missing activity are
14 also there.

15 We are trying to re-encourage people to
16 take a look at accelerated approval as it was
17 meant, that there would be randomized trials that
18 were ongoing in a reasonable indication such as a
19 first-line indication, and if it looked like their
20 drug was better in a randomized setting against the
21 standard therapy, they would get approved on a
22 surrogate endpoint, awaiting survival data to come
23 up.

24 But this is a manifestation I think of
25 companies looking at what are niche areas to get

1 their drug approved on a single-arm trial and we
2 really are trying to discourage that to get more
3 randomized trials in place. It gives better
4 characteristics as far as toxicities of the
5 therapies. We actually get the drug approved in an
6 indication that is meaningful.

7 DR. ELIAS: I am sorry, these are
8 randomized trials. I mean, there is nothing wrong
9 with the science or anything like that. But what I
10 do find difficulty with is just that by the time
11 you get to a mandate to be able to use experimental
12 therapies you have already exhausted all of your
13 standard approaches. That, at least
14 philosophically, I think is the wrong way to go
15 about it.

16 DR. LEVIN: And those can be mediocre
17 therapies.

18 DR. ELIAS: Yes.

19 DR. BENJAMIN: But this issue is not an
20 FDA issue. This is an insurance reimbursement
21 issue. The problem is the way medical care is paid
22 for and the pediatricians have learned the right
23 way. They do have a monopoly. Everybody goes on
24 trial and it gets paid for. The adult oncology
25 community has not learned how to do that. So, the

1 only things that get paid for are the
2 non-experimental treatments and that encourages an
3 anti-clinical trial approach. So, I think that is
4 not an issue that we can solve here.

5 DR. SANTANA: I think we were commenting
6 on that same thing on this side of the table, that
7 the issue is that pediatrics is a completely
8 different model of how to surmount some of these
9 problems.

10 Questions

11 I want to go ahead and get to the
12 questions before we go to lunch because, if not,
13 the FDA will tell me I haven't done my job. So,
14 let's go ahead and address the questions. They are
15 on the second page of the handout. Some of these I
16 think we may have already answered but we will go
17 through them.

18 Specifically for sarcomas, which is what
19 we have been discussing for the last two hours,
20 what general principles could be used to relate
21 sarcomas in adults to sarcomas in children? Mike?

22 DR. LINK: I think I would endorse your
23 extra slide, your spare slide, as sort of a
24 starting point, you know, that if we can define a
25 molecular basis, which is a unifying theme, that we

1 should take advantage of it.

2 DR. SANTANA: I would go a step back and I
3 would say that I think for sarcomas still the issue
4 of histology, grade and molecular characterization,
5 in that order, are the principles that define the
6 similarities and the differences. I am taking what
7 you said and extending it a little bit further.
8 David?

9 DR. PARHAM: I would emphasize grade over
10 histology because I think grade is sort of an
11 expression of biologic status of that tumor using
12 morphologic parameters. So, to me, that should be
13 one of the overriding things because a low grade
14 tumor, if completely excised, is cured. A high
15 grade tumor, even if completely excised, probably
16 deserves additional therapy. I know there are some
17 caveats between grading pediatric tumors and
18 grading adult tumors but I don't think these should
19 exclude the possibility that it cannot be done and
20 that we should really concentrate on grading
21 sarcomas in order to stratify them for new
22 therapies, given the fact that a large proportion
23 will be cured adequately by surgery.

24 DR. FINKLESTEIN: I am not the scientist
25 that is sitting around this table but it seems to

1 me that I have to disagree with my colleague to my
2 left -- both colleagues to the left because if we
3 are really talking about new generation, it seems
4 to me the microscope may have played a significant
5 role in the past but is not molecular biology the
6 role for the present? And, is grade moving
7 backwards and molecular biology moving forwards or
8 is it vice versa?

9 So, I do like Steve's slide. I think
10 there is a role -- I can give you an example.
11 Embryonal rhabdomyosarcoma, if it sits in the
12 bladder, looks like grapes and if it sits somewhere
13 else -- and you will have to correct me, Mike, if I
14 am wrong -- and it may be the same molecular lesion
15 but if it sits somewhere else it is going to look
16 different. Grossly it will. So, I really would
17 like us to reconsider do we use the microscope or
18 do we use and call upon our molecular biologists
19 for the present and the future?

20 DR. SANTANA: Jerry, I think my comment is
21 that they are complementary because we know a lot
22 about the former; we are just beginning to learn
23 about the latter and how it correlates to the
24 former. So, I don't think they are exclusive; they
25 are complementary. And, you may be right, we know

1 a lot more about the molecular characterization of
2 alveolar rhabdomyosarcoma but we still don't know
3 what that means in terms of what drugs we should be
4 using for those patients. So, that is why my
5 comment was more of complementary, not abandoning
6 one and bringing a new one forward. Bob?

7 DR. BENJAMIN: Yes, actually, Victor, I
8 would like to support your contention. I think we
9 may get to molecular definition and that is well
10 and good, but we don't have molecular definition
11 for most of the tumors that we treat.

12 But I would strongly disagree with Dr.
13 Parham that grade by itself unifies. Grade unifies
14 aggressive behavior. High grade osteosarcoma and
15 high grade embryonal rhabdomyosarcoma are totally
16 different diseases. They are treated with
17 different drugs; they respond differently. If we
18 just say, well, everything high grade gets mixture
19 A-B-C we are going to mix the things which are
20 important. We know that there are differences in
21 these tumors that are based on their biology and
22 right now the best definition of the biology is
23 what it looks like under the microscope.

24 DR. SANTANA: Mike?

25 DR. LINK: Yes, I think that we are

1 quibbling over something which is probably not
2 useful because grade is irrelevant in
3 rhabdomyosarcoma. You know, I mean we can argue
4 this some other time but it is certainly
5 irrelevant. It is very relevant in osteosarcoma
6 but we all acknowledge that those are different
7 diseases when you have a periosteal osteosarcoma.
8 So, it is relevant in a group of tumors which is
9 very unlikely to occur in children. So, in the
10 soft tissue sarcomas where there is no molecular
11 definition, which are the diseases that actually
12 don't occur in children anyway so it is a
13 non-issue, you can use whatever it takes. But the
14 point is that where we have actually got the
15 tissues and we have the diagnosis -- and we are not
16 going to say that the pathologists -- I think you
17 are taking it a little too far, Jerry, to say that
18 the pathologist has out-served his -- first of all,
19 we will never get another tissue sent for another
20 study ever again --

21 [Laughter]

22 So, what was it? delicate politics or
23 diplomatic? Even I recognize that that wouldn't
24 have been approach and I am not known for my
25 delicate politics particularly. So, I wouldn't

1 have said that, but I think that we have a fairly
2 good one from our chairman that, you know, we have
3 to encompass everything that is important and where
4 we have the molecular things and we have an agent
5 that really is related to the molecular event, then
6 obviously that is paramount. When we are talking
7 about an agent that has more to do with grade or
8 more to do with proliferative rate for which there
9 may be an agent, that is the unifying thing rather
10 than a particular kinase that it inhibits. Then
11 maybe grade will be the paramount thing in terms of
12 determining where it should be studied.

13 DR. FINKLESTEIN: I accept your diplomatic
14 interpretation of my remarks.

15 [Laughter]

16 DR. SANTANA: That is the other difference
17 between pediatricians and adult oncologists!
18 Larry?

19 DR. KUN: There are differences here and
20 one of our charges -- I mean, if you look at is it
21 appropriate to study new agents, then grade is
22 clearly an indicator of prognosis. On the other
23 hand, if you are really looking at how you identify
24 new agents, it might be applicable or justified for
25 a particular new agent, then grade is almost

1 meaningless. I mean, it may be quite important in
2 your initial prognosis but it is not going to
3 determine what agent you are anxious to try.

4 DR. POMEROY: I would like to add that the
5 issue of obtaining tissue for developing a
6 molecular taxonomy is not a trivial one, as my
7 pediatric brain tumor colleagues will attest in our
8 recent meetings. If there are diseases, which is
9 true for all pediatric brain tumors at this point,
10 where you don't have a molecular marker that
11 impacts a treatment decision, then so far it has
12 not been mandated that we collect tissue to be part
13 of a clinical trial.

14 In the current ethical and regulatory
15 environment, it sounds like we are going more in
16 the direction that we need consent, we need to have
17 approval to be able to collect these tissues and we
18 cannot ethically put patients on trials where we
19 don't have a decision to be made for collecting
20 their tissue with tissue collection as mandatory
21 because that would be coercing them to give tissue
22 to get treatment when they don't have any tangible
23 benefit for themselves. So it is a tricky issue
24 that we have been struggling with a lot in
25 pediatric brain tumors and I can only imagine in

1 all tumors as well.

2 DR. SANTANA: Paul?

3 DR. MEYERS: It is not quite as ethically
4 suspect as that. If you are talking about a Phase
5 III trial which involves conventional agents, then
6 denying a patient participation in the trial is not
7 denying them potential benefit. They can have all
8 of those agents without trial participation. So,
9 in fact, for the osteosarcoma and the Ewing's
10 sarcoma trials we have required specimen submission
11 for entry into the clinical trial. If they decline
12 to submit tissue we are not denying a child
13 potential benefit. They can receive all of the
14 therapy according to but not enrolled in the trial.
15 In fact, with this particular strategy we surprised
16 ourselves with the increase in the amount of tissue
17 submission in both of those clinical entities. We
18 are now getting excellent submission of biological
19 material.

20 I do think we are just a tiny bit off the
21 topic though because the question was what
22 principles should we be using to relate sarcomas in
23 children and adults, and I think that they are
24 stated, that we should use histology and molecular
25 pathology, but I have not heard anyone disagree

1 with the principle that we should encourage, design
2 and carry out trials which ignore the age of the
3 patient as much as possible and concentrate on the
4 biology of the tumor.

5 DR. SANTANA: Donna?

6 DR. PRZEPIORKA: Actually, that was almost
7 essentially the comment that I wanted to make and
8 both speakers very eloquently stated that an
9 osteosarcoma in a kid isn't like an osteosarcoma in
10 an adult, and no one has presented any information
11 that sarcomas in children are different than
12 sarcomas in adults if you get down to the
13 histology. Even if we go on to question B, any
14 specific type of sarcoma doesn't appear to be --
15 or, there was no data presented to suggest that
16 different types of sarcoma are different in adults
17 and pediatric patients, unless anybody has any
18 other information that wasn't stated.

19 DR. SANTANA: Because nobody disagrees, we
20 have actually covered A and B together. Mike?

21 DR. LINK: I agree. I just want to say
22 that the caveat is that, as a statistician would
23 say, no difference doesn't mean that there is no
24 difference. It just means you haven't detected it.
25 So, we know that older patients do less well.

1 There is a bunch of theoretical reasons why that
2 is, you know, blaming the oncologist and blaming
3 the tumor and everything in between. But it may be
4 the tumor and I think that until we have array data
5 that shows that they really are identical, that all
6 the downstream effects of having that EWS-FLY1
7 transcript are the same in an older patient and a
8 younger patient I don't think that you can -- I am
9 not as certain because there has to be some reason
10 why an 18-year old treated by a pediatric
11 oncologist in the same center as a 10-year old does
12 less well. Then, remember, the IRSG data that I
13 showed you, those aren't patients that are treated
14 by adult oncologists. Those are patients treated
15 in the same centers, by the same people, with the
16 same willingness and putatively the same compliance
17 with therapy, although that is an issue -- not
18 entirely the same host but we think that there is
19 not much difference between an 18-year old and a
20 12-year old in terms of their tolerance for
21 therapy, yet the outcome is quite different.

22 So, I think that you may or may not be
23 right, but I think I still agree with Victor. You
24 know, I don't think that changes the answer to the
25 question.

1 DR. HIRSCHFELD: Then the question, once
2 again, is when should studies be undertaken, not
3 when should the therapy necessarily have findings
4 extrapolated from one population to another but
5 should it be studied.

6 DR. SANTANA: So, I think we have answered
7 A and B, unless Steve or Richard want to address
8 the issue differently.

9 DR. BENJAMIN: Well, I think that
10 rhabdomyosarcoma needs to be studied specifically
11 in a pediatric population because that is where it
12 exists.

13 DR. SANTANA: Oh, yes.

14 DR. BENJAMIN: And, I would be happy to
15 include adults on the pediatric trial but it is a
16 pediatric disease and we are not going to be able
17 to study it in adults. There must be studies in
18 children on these tumors. For Ewing's
19 osteosarcoma, you know, they go across the bridge.
20 We are going to continue to study them. I think we
21 should study them in the same way and learn
22 whether, in fact, we can determine what the factors
23 are which make the 18-year old different from the
24 10-year old. But I am certainly not going to treat
25 the 18-year old patient with rhabdomyosarcoma on an

1 osteosarcoma protocol because he is 18. I mean,
2 his therapy is determined by the disease.

3 DR. SANTANA: We agree. The last
4 question, I had trouble with this one, Steve. You
5 may have to give us some more guidance in trying to
6 answer this. So, are there pediatric sarcomas that
7 have an adult counterpart that is not commonly
8 defined as an adult sarcoma but as some other type
9 of adult malignancy such as carcinoma? Help me
10 through that. What do you want from us on that?

11 DR. HIRSCHFELD: Okay. Every once in a
12 while, because of historical reasons or taxonomic
13 reasons based on histology, a disease ends up with
14 a different name. So, since we asked about
15 extrapolation from adult sarcoma to pediatric
16 sarcoma, we wanted to look at the obverse question,
17 is there a pediatric sarcoma that, now that we have
18 a different understanding of biology, has some
19 other name?

20 I will give a potential example. A
21 potential example might be the GI leiomyosarcomas
22 which have been called different things in
23 different eras and now we might think of it as
24 something different. So, we just wanted to make
25 sure that if we are reviewing proposals from

1 companies and they say they want to cover tumor X
2 that we would say, oh, well, we were advised every
3 time we saw tumor X to think that there also might
4 be a role for asking for pediatric studies. So, it
5 is just an attempt to be complete.

6 DR. SANTANA: Others may want to comment;
7 I don't have any comment. David?

8 DR. PARHAM: Dr. Benjamin actually raised
9 that question indirectly because we do have an
10 adult tumor, which is rhabdomyosarcoma, pleomorphic
11 rhabdomyosarcoma, and that diagnosis has gone in
12 and out of favor. But I think from a biologic
13 basis they are nothing like pediatric tumors but I
14 would bet that question as to whether you would put
15 those tumors on a rhabdomyosarcoma program. They
16 are really defined only by the fact that they make
17 muscle but biologically they are different.

18 DR. BENJAMIN: But I think that is also
19 true of embryonal and alveolar. That is one of the
20 reasons why some of the differences in the older
21 rhabdomyosarcoma patients come out, because there
22 is a higher percentage of the bad-acting group, but
23 the bad-acting group is defined as the bad-acting
24 on the therapy given for the entire group. It may
25 well be that we need different therapy for alveolar

1 rhabdomyosarcoma than we need for embryonal
2 rhabdomyosarcoma, and alveolar can be defined
3 molecularly so that is a group that needs specific
4 targets.

5 I agree completely with you about the
6 pleomorphic. I don't know how many of them you see
7 in pediatrics. We see relatively few still in
8 adults, at least at Anderson. Again, that depends
9 on definitions and what you accept as the
10 definition of pleomorphic rhabdomyosarcoma. I
11 mean, we do see some and, frankly, we treat them
12 more like an adult sarcoma. You are right. We
13 would like a pediatric rhabdo.

14 DR. HIRSCHFELD: I would like, Victor, to
15 have just one clarification before we break for
16 lunch, and that is in part B, number 4. I just
17 want to make sure that we are not being too
18 efficient. Specifically, should gastrointestinal
19 carcinomas be excluded or included? I just want a
20 little discussion on that point.

21 DR. LINK: Colon cancer?

22 DR. HIRSCHFELD: Or stomach cancer, yes.

23 DR. SANTANA: A rare entity, Steve.

24 DR. HIRSCHFELD: No, no, I want it
25 addressed. What we are looking for here is if

1 someone comes in and says we are studying a
2 gastrointestinal carcinoma, that we would be
3 comfortable saying no, we have advice and we feel
4 that there is no mandate for pediatric studies,
5 that this should be waived.

6 DR. SANTANA: I think 4 specifically are
7 very, very diseases --

8 DR. HIRSCHFELD: But not in adults.

9 DR. SANTANA: In kids. That is what I am
10 telling you. So, in terms of attributing the
11 waiver, it has to apply. It is just a very few
12 number of patients.

13 DR. HIRSCHFELD: Right.

14 DR. SANTANA: Logically, I would have to
15 assume, and I may be incorrect both in my logic and
16 my assumption -- logically, I would have to assume
17 that the counterpart is the adult disease.
18 Anthony?

19 DR. ELIAS: Just one caveat to that,
20 namely, if you are talking about chemoprevention of
21 gastrointestinal tumors in familial syndromes, for
22 example, there certainly may be a rationale for
23 that particular situation to want to be able to
24 study children as well. But otherwise I totally
25 agree that the actual carcinoma is not a pediatric

1 disease.

2 DR. SANTANA: That is a very good point,
3 Anthony. Yes, that is a very good point. Donna?

4 DR. PRZEPIORKA: The other situation is
5 biologics and inhibitors of biologic markers,
6 addressing C in a slightly different approach in
7 that if you have a gastrointestinal tumor with a
8 specific tyrosine kinase and that tyrosine kinase
9 is also present in another pediatric tumor and does
10 the same thing, that inhibitor should probably be
11 tested in pediatric patients. For example, the
12 PDGF inhibitors are being tested now in prostate
13 cancer. There is no prostate cancer in kids but,
14 clearly, PDGF is a big thing in pediatric tumors.
15 So, yes, that drug should be tested in pediatrics.

16 DR. SANTANA: But ultimately the end
17 result is what is the medical indication being
18 sought that would drive that. Am I correct?

19 DR. HIRSCHFELD: It is going to depend on
20 how we, again, define the word "indication."
21 Although conventionally we have stuck to histologic
22 definitions, we are open and evolving in terms of
23 how we define that.

24 DR. LINK: But isn't that circumstance a
25 little bit of a non-issue because putatively if you

1 have shown that it works in a pediatric tumor you
2 have already studied it in kids, and then you want
3 to open the indication up to adult tumors. Maybe I
4 have it wrong. The other way around? All right, I
5 withdraw my comment.

6 DR. BENJAMIN: But the comment regarding
7 the PDGF inhibition is that we do not know in which
8 circumstances PDGF is the critical driving factor
9 of the malignancy. We know that it is present in a
10 number of different tumors of vastly different
11 histology. We also know that c-Kit is present in a
12 number of tumors of vastly different histology. We
13 don't know that inhibition does anything except
14 just where c-Kit is critical to the development of
15 the tumor. It may or may not; it may work in some
16 and not others. We may find out that PDGF is
17 present in osteosarcoma and in Ewing's sarcoma but
18 that blocking it has an effect in osteosarcoma and
19 not in Ewing's sarcoma. We need to do all of those
20 studies to find out, and we may come back a few
21 years from now and say, okay, we know that this
22 pathway, if it is ever blocked, will always be
23 therapeutic and we can define an indication based
24 on a pathway. But until we have the data I don't
25 think we can say that.

1 DR. SANTANA: Pat?

2 DR. REYNOLDS: I think with respect to
3 that issue the pediatric preclinical testing
4 consortium that Malcolm spoke about is going to be
5 a valuable asset to providing data, and if there
6 was consideration from FDA as to whether or not
7 they should grant a waiver and there was a common
8 target among pediatric tumors, presumably that
9 consortium could quickly address that and tell you
10 if there was preclinical basis for saying no, this
11 should be studied or there was a lack of
12 preclinical data and, therefore, a waiver should be
13 amended.

14 DR. SANTANA: Dave?

15 DR. POPLACK: I think that Steven quite
16 eloquently represented that in his slide, that the
17 presence of a common pathway doesn't make or define
18 the need for a trial. There has to be a definition
19 which encompasses that the pathway is related to
20 the development and progression of the disease.

21 DR. SANTANA: Howard?

22 DR. FINE: And that just bets the issue
23 that I often talk about. Some of us do believe
24 that as molecular targeting becomes more than just
25 a catch-all phrase but becomes a reality, there

1 will be drugs ultimately, hopefully, that will be
2 approved based on their target rather than their
3 histologic subtype in the future, but that gets
4 down to this term we talk about as far as target
5 validation. The mere presence of a target is very
6 different from target validation. Again, that gets
7 back to what I spoke about before. I think that is
8 where the academic investigators -- it is incumbent
9 upon you if you are interested in a particular
10 tumor type, such as a pediatric tumor, it is
11 incumbent upon us to validate that target in order
12 to make a case for that drug to come into trial.

13 DR. SANTANA: Last comment, Joe?

14 DR. GOOTENBERG: From the biologics
15 viewpoint, what we are really talking about here --
16 and from a drug viewpoint also but biologics I
17 think is where we are going to come into these
18 issues -- we are talking about one narrow question.
19 When a manufacturer comes in and says they want a
20 license whether or not we grant them a waiver for
21 doing pediatric studies, not licensing or this or
22 that, and the question that I think, Donna, you
23 posed very well and that we would like some
24 consensus on from the group would be that if there
25 is a common pathway but the two diseases are very,

1 very different historically should we or should we
2 not grant the waiver? Just like the PDGF that you
3 are talking about.

4 DR. PRZEPIORKA: The answer would be no.

5 DR. SANTANA: Anybody disagree with that?

6 [No response]

7 Then we are done for the morning. We will
8 try to reconvene at 12:45. It says 12:30 on the
9 schedule but since we ran a little bit late we will
10 meet at 12:45.

11 [Whereupon, at 12:00 noon, the proceedings
12 were recessed, to be resumed at 1:58 p.m.]

1 [Slide]

2 Starting off by looking at the different
3 histological types of lung cancers, there are
4 different ways you can approach it but one common
5 way is to separate out these lung tumors into
6 neuroendocrine lung tumors and non-neuroendocrine
7 lung tumors. Of the neuroendocrine lung tumors the
8 most common type is small cell lung cancer. I
9 might add that the term for small cell may be a
10 little bit of a historical term because it is also
11 called oat cell carcinoma. There is some feeling
12 that at least part of that might have been crush
13 artifact. These cells are very fragile in general,
14 and they have a tendency for crush artifact on the
15 edges. I know Dr. Matthews, who is a
16 well-respected lung cancer pathologist over at NIH,
17 felt that many of these tumors were medium sized
18 epithelial carcinomas and the oat cell phenotype
19 might have been contributed by crush artifact.

20 At any rate, the one distinguishing
21 feature that we had noted in our lab about a decade
22 ago is that small cell lung cancers were very
23 tightly correlated with RB gene inactivation. This
24 is unusual because there is almost no other tumor,
25 that is, besides the pediatric retinoblastoma tumor

1 and then, in the case of a subset of sarcomas that
2 might arise in the phenotype of familial
3 retinoblastoma. So, it is distinctly unusual to
4 see a tumor that will have in excess of 90 percent
5 have mutationally targeted the RB gene.

6 Now, other common types of neuroendocrine
7 lung tumors are pulmonary carcinoid tumors,
8 non-small cell lung cancer with neuroendocrine
9 phenotype -- these are usually called large cell
10 tumors with neuroendocrine phenotype but they can
11 be in almost any histological type of non-small
12 cell. The feeling is that since this is the
13 largest subtype of lung cancer seen in about 10
14 percent of these lung tumors have striking markers
15 for neuroendocrine phenotype, there was a sense of,
16 well, how do you distinguish these tumors from
17 small cell lung cancer, and perhaps they may have
18 similar biological features, response to treatment,
19 etc.

20 That really hasn't resolved itself. They
21 do have distinct, it appears, genetic background
22 from small cell lung cancer, and the response to
23 treatment is higher but not quite like small cell.
24 So, there is some confusion as to exactly what the
25 meaning is of non-small cell lung cancer with

1 neuroendocrine phenotype and it gets back to the
2 cell of origin of these tumors. There is still
3 some controversy as to whether or not there might
4 be a stem cell that is targeted that can
5 differentiate into different types of lineages that
6 might include neuroendocrine and non-neuroendocrine
7 types or the specialized differentiated cell is the
8 one that is targeted for the mutational events.

9 This is partly driven by the fact that
10 pathologists have seen different histological types
11 of lung cancer in the same tumor biopsy, where they
12 might see tumor types that will have small cell
13 features along with either squamous or
14 adenocarcinoma. It is not a large number but there
15 is a small subset.

16 These are the main types that are thought
17 to be lung tumors. There are other types that
18 might be included. The ones that I put up there
19 are primary undifferentiated carcinomas and, of
20 course, peanut type tumors tend to occur in
21 non-smokers and in younger patient types, and some
22 of them may have, if we look for them,
23 characteristic molecular characterizations that
24 might put them into other categories. Nonetheless,
25 since they have neuroendocrine features and since

1 we are not exactly sure how best to manage them,
2 and many of these patients can present with
3 metastatic disease just like small cell lung
4 cancer, there has been a sense that as long as the
5 lung tumor has a neuroendocrine phenotype there is
6 a certain aggressive biological behavior associated
7 with it, with the exception of typical pulmonary
8 carcinoid. There are certain chemotherapy drugs,
9 mainly of the cisplatin category, that are utilized
10 for treatment.

11 Of course, there is carcinoid of unknown
12 primary that can sometimes have neuroendocrine
13 phenotype or germ cell type element that can be
14 central or mediastinal, and those are also often
15 recommended to be lumped together to treat them
16 with small cell lung cancer-like regimens.

17 I put up here just for interest that there
18 are few clearly small cell lung cancer-related
19 diseases which are non-lung tumors. The best
20 characterized are what we call extrapulmonary small
21 cell. Small cell lung cancer -- and we have seen
22 it and maybe a number of pathologists have seen it
23 -- can arise primarily in the prostate gland; in
24 the bladder; in the cervix; in the thyroid and a
25 variety of other organ tissues. They are not

1 common but when they do appear they seem to have a
2 lot of biological features and they include the
3 characteristic feature of mutationally inactivating
4 the RB gene. So, there is a close connection with
5 this, and why they are arising in other tissues and
6 not in the lung is still uncertain.

7 The other tumor type is Merkel cell tumor,
8 which is a characteristic cutaneous tumor but it is
9 highly aggressive and even though it might present
10 locally in the skin, we often recommend that after
11 that is excised that they receive a small cell lung
12 cancer type regimen.

13 The other box I included there is purely
14 animal model type information. Using the clue that
15 the small cell lung cancer has unusually targeted
16 in almost every case the RB gene, if you make a
17 mouse that is defective for the RB gene and in that
18 sense make a familial retinoblastoma mouse, the
19 mouse doesn't develop retinoblastoma tumor although
20 you can under other experimental circumstances.

21 But, what the mouse gets is a series of
22 neuroendocrine tumors which are really fascinating
23 and is a subject of some work, and they get
24 spectral tumors which overlap between the MEN1 and
25 MEN2 syndromes. They certainly get pituitary

1 tumors with almost 100 percent penetrance, but they
2 will also get medullary thyroid cancers. They will
3 get islet cell tumors of the pancreas. They will
4 get pheochromocytomas, etc.

5 So, there is an important link there with
6 mutationally targeting the retinoblastoma gene and
7 even though the RB gene is essential for transit
8 through the cell cycle in all eukaryotic cells,
9 there is something specific about it as a single
10 hit leading to retinoblastoma tumors in humans,
11 which is a neuroendocrine tumor which does resemble
12 in cell culture and other things in retinoblastoma.
13 But also in animal models it is telling us that
14 there is an important link that is still undefined.

15 [Slide]

16 I am saying lung tumors because many of
17 these aren't considered lung cancer but they are
18 tumors that arise in the lung -- taking just the
19 malignancy ones and not benign lesions, of course,
20 the most common is what is called non-small cell
21 lung cancer, just the general category of many
22 different histologic types -- adenocarcinoma, the
23 squamous cell, large cell undifferentiated are the
24 most common type.

25 I put bronchoalveolar carcinoma as an

1 additional one because even though histologically
2 it belongs to adenocarcinoma, it has a number of
3 very distinct clinical features, although also some
4 histologic features.

5 As I said, about 10 percent of these
6 non-small cell lung cancers will have a
7 neuroendocrine phenotype. They will appear maybe
8 as two different populations or as a population
9 that partially resembles neuroendocrine cells, and
10 they will especially express a number of markers.
11 It is very popular to use synoptifisine and a
12 variety of other neuroendocrine markers to tell
13 this.

14 There is some thought that maybe this
15 could guide treatment, and there is a push to
16 perhaps consider cisplatin-like regimens although
17 these regimens are pretty much used routinely now
18 for all types of lung cancer. So, that is really
19 not as much of an issue as it was five or ten years
20 ago.

21 Mesothelioma is a very different type of
22 lung tumor. It is of interest to us because it
23 will have a specific genetic marker that will help
24 in molecular diagnosis and that should be coming
25 out in the future.

1 There is pleuro-pulmonary blastoma which
2 is primarily a pediatric disease. Then, of course,
3 there are sarcomas of a variety of types that can
4 occur primary to lung but they are unusual and we
5 might see only an occasional patient a year.

6 [Slide]

7 I will just jump ahead and just show one
8 slide on the RB gene because it makes a few
9 important points. First of all, identifying that
10 about 90 percent, or slightly in excess, of small
11 cell lung cancers have targeted the RB gene for
12 mutational inactivation, and these can be just
13 single codon substitutions, but the biochemical
14 result is that they function as null. It is as if
15 they weren't there.

16 One interest we had in the lab is that
17 there are about five or ten percent of small cells
18 that still retain wild type RB function. We
19 thought it may be a DNA tumor virus or a variety of
20 other exogenous that might be targeting it. It
21 turned out that an upstream gene, called the p16
22 gene, was the one that was mutating those. When we
23 went back to look at non-small cell lung cancer we
24 found that almost all of non-small cell lung cancer
25 had targeted the p16 gene and not RB. Small cells

1 target RB and not p16. They both target the same
2 pathway that is referred to as the RB/p16 pathway.
3 You only need to knock out one or the other but not
4 both. So, 100 percent of lung cancers are
5 targeting this pathway. It is still the undefined
6 question as to why this neuroendocrine type is
7 picking RB gene while the non-neuroendocrines pick
8 p16.

9 This pathway is particularly interesting
10 because it converges on a set of enzymes that by
11 themselves will entirely drive the cell cycle,
12 particularly the transition between G1S and then
13 the transition through mitosis as well, and this is
14 the cyclin-dependent kinase family. A variety of
15 other epithelial tumors -- you can find in
16 melanoma, for instance, a specific mutation in a
17 cyclin-dependent kinase molecule. That is shown on
18 the slide as CDK. The mutation is exclusively at
19 the site where the p16 inhibitor will bind to CDK.
20 So, when you mutate the CDK molecule, its enzyme
21 kinase activity is completely intact. But what it
22 can no longer do, it can no longer bind to p16.
23 So, it is as if p16 wasn't present. So, it
24 resembles other tumors where p16 has been mutated.

25 When you look at these tumors you find

1 that RB is wild type, p16 is wild type, but the
2 single mutation is in this one residue on the
3 cyclin-dependent kinase molecule. So, this shows
4 you that while there is really an RB, CDK, p16
5 pathway, you only need to mutate one but not any of
6 the other ones to disrupt the pathway. And,
7 certain melanomas will target CDK. Other melanomas
8 will target p16 non-small cell lung cancer, and
9 many other cancers will target p16. Small cell
10 lung cancer targets RB.

11 Finally, cyclin-D is the other partner in
12 this, and cyclin-D overexpression has been noted.
13 As a matter of fact, it was first identified as a
14 translocation partner in parathyroid tumors and it
15 was initially called the Prad-1 gene. It has also
16 been found in a number of other circumstances,
17 BCL1. In breast cancer it is overexpressed. In
18 those where it is overexpressed, it appears again
19 as if that is the only target in this whole
20 pathway.

21 That is again particularly interesting
22 because there is a series of papers, one that was
23 reported yesterday, in which you look, again, in
24 animal models which tell us a lot. Looking at the
25 tumor patterns to identify these pathways are so

1 much more precise, I believe, than in vitro
2 laboratory experiments, and when you look at a
3 mouse model, they have known for about five or six
4 years that you can have a cyclin-D1 null mouse and
5 that mouse grows up normally without any tumors.
6 It has a few other really specific histological
7 abnormalities but when they cross the cyclin-D1
8 mouse with a transgene mouse that gives a high
9 penetrance for breast cancers -- when they cross it
10 with a ras transgene mouse that will give you
11 breast cancers in a wild type background otherwise,
12 when they cross in a cyclin-D1 null mouse you get
13 no breast cancers. So, it is strongly arguing that
14 this mutated ras is acting again through a
15 CDK-cyclin-D1 pathway and that gives important
16 clues.

17 When they take a neu mouse, which is
18 another word for the Her2 neu since neu was
19 originally described in neuroblastoma tumor, that
20 also gives a high penetrance of breast cancers.
21 When they cross that with a cyclin-D1 null mouse,
22 they get no breast cancers, again arguing that at
23 least a new pathway appears to be also funneling
24 in, in some way to cyclin-D1.

25 On the other hand, when they crossed that

1 with a classic myc transgene mouse that give a high
2 incidence of mammary tumors, they saw no reduction
3 in the number of breast tumors in the cyclin-D1
4 null mouse. So, it is giving some clues and using
5 this key point of the G1S phase as a funnel but,
6 again, giving some clues as to different pathways
7 and perhaps now incorporating ras, neu and other
8 things. That is sort of a general editorial
9 comment.

10 [Slide]

11 So getting back to adult lung cancer, a
12 number of labs -- our lab and other labs have tried
13 to collect what might be some defining phenotypes,
14 and there are a number of caveats with this. One
15 caveat I might add is instead of myc overexpression
16 it is myc amplification of one of the different
17 members. Myc overexpression will be considerably
18 higher.

19 But, again, there are also caveats with a
20 number of these percentages put here but they give
21 a rough idea, showing how small cell lung cancer,
22 the neuroendocrine, is genetically different from
23 non-small cell lung cancer. If you look at certain
24 genes, they are very similar when you look at other
25 genes. Certainly, small cell lung cancer is very

1 different from other lung neuroendocrine tumors
2 such as carcinoid if you look at some genes but not
3 others.

4 [Slide]

5 This shows the genes which are probably
6 best implicated in lung cancer, RB, p16, CDK-cyclin
7 pathway -- myc, there seems to be, I think,
8 substantial strong circumstantial evidence,
9 likewise for ras, p53. Also, I believe for p10
10 signal transduction pathway and perhaps for erbB.

11 All these tumors are notably characterized
12 by chromosomal instability and have a high
13 incidence of telomerase activation. On the right
14 side there is a long list of many other candidate
15 lung cancer genes, particularly candidate genes on
16 the short arm of chromosome 3. I might add that
17 c-Kit is activated in a large number of these lung
18 tumors but, as far as I can tell -- I am not
19 involved in these studies, there really haven't
20 been dramatic responses with the Gleevec agent but
21 I am not the source to report on that.

22 [Slide]

23 I am going to end right there just with a
24 brief introduction, and these are just some
25 off-the-cuff thoughts I had when I sent in the

1 slides yesterday. Extrapolation will need to focus
2 on cell biology and genetics. As has been
3 mentioned here before, you know, assuming that we
4 know enough for rational therapies, the specific
5 treatment.

6 The overwhelming thing that hits you when
7 you look at lung cancers is the neuroendocrine
8 phenotype because they do appear to be a
9 characteristic feature of a large number of adult
10 lung cancers. If you take small cell lung cancer
11 by itself, they say it would be the fourth or fifth
12 most common cancer. But this decision, as I say,
13 would require a case by case evaluation. I suppose
14 that is part of what this committee is here for, to
15 look at that.

16 If you take specific treatments you can
17 decide with it is one of these unusual fusion
18 translocations that you only see in a certain type
19 of tumor, like in some of the subsets of sarcomas
20 etc., or you can take something like the p53 gene
21 which is seen in almost all epithelial cancers and
22 my sense is if there were a way to express wild
23 type p53 function in these tumors, you would stop
24 them and you would induce either growth arrest or
25 cell death very consistently, and that would be an

1 overwhelming choice, just in my opinion. So, if
2 you had a therapy that you could consistently show
3 would reactivate wild type p53 functioning cells,
4 that would be a good choice for a whole range of
5 what you might otherwise think are disparate
6 histologic subtypes. That doesn't exist right now
7 but the hope will be that APL, which is probably
8 the best paradigm because there is a certain type
9 of treatment linked with a certain translocation,
10 might be applicable.

11 One last sort of side comment, and this
12 has to do with the discussion that we had before
13 about molecular diagnostics in sarcoma, I just want
14 to emphasize, not as a pediatrician and not working
15 in sarcoma, that I feel that it really is
16 critically important to get the molecular
17 information despite the practical issues, and I am
18 sure in brain cancer they are exponentially
19 important. But if you look even in the APL
20 situation, as far as I understand it, there are a
21 number of different types of translocations that
22 can be seen in APL with different binding partners,
23 and not all APL leukemias respond to retinoic acid
24 and there is some suggestion that the specific
25 translocation in APL is the one that really will

1 target to you which ones of those APLs will respond
2 to retinoic acid. Using that, again, as a
3 paradigm, it continues to emphasize the need to be
4 collecting this data and putting it into the
5 database.

6 Then, the last thing is that these are
7 still the tentative days of directed treatments, as
8 has been pointed out here before. There is a track
9 record of empirical success, and we just have to
10 keep in mind that a lot of our rational therapies
11 will appear empirical down the road. Thanks.

12 DR. SANTANA: I think we will have time
13 for discussion and questions later. I want to ask
14 Pat Reynolds to discuss issues of neuroblastoma as
15 they may relate to some adult counterparts.

16 Neuroblastoma and Small Cell Carcinoma of the Lung:

17 Differences and Similarities

18 DR. REYNOLDS: I would like to thank Vic
19 and Steve and Karen for asking me to talk on this
20 topic. This particular topic is one that has
21 fascinated me since I was a medical student, and
22 that is really, is there any relationship between
23 small cell carcinoma of the lung, a tumor that
24 occurs in older adults, and a pediatric tumor, a
25 neuroblastoma?

1 I work at a children's hospital and I
2 couldn't find any of my colleagues to make any
3 profound statements about lung cancer --

4 [Laughter]

5 [Slide]

6 -- but since my children's hospital is
7 located in Hollywood, I relied on some of the local
8 talent to point out to us that lung cancer is
9 primarily a disease of smokers.

10 [Laughter]

11 That is clearly one of the major
12 differences between neuroblastoma and small cell
13 lung cancer, and that is that it is a disease in
14 which the etiology of small cell cancer is almost
15 exclusively related to tobacco use whereas,
16 clearly, that is not related, at least as far as we
17 know, in any way to the etiology of neuroblastoma.

18 [Slide]

19 These tumors share a common ancestor. If
20 you look on this rather complex slide, the neural
21 crest stem cell gives rise to a whole variety of
22 different neuroendocrine cells within the body. In
23 fact, it is this ability that is required of the
24 neural crest stem cell to migrate out and spread
25 throughout the body that is thought to confer some

1 of the biological features of tumors derived from
2 the neural crest stem cell, namely, the propensity
3 for rapid and widespread metastasis early in the
4 course of progression. That is certainly true for
5 neuroblastoma and small cell lung cancer, as you
6 will see.

7 Neuroblastoma probably arises from the
8 neural crest stem cell, or from a cell that is just
9 immediately downstream from it, because there is a
10 variety of these different phenotypes that can come
11 out in a differentiated pattern from neuroblastoma.
12 Small cell lung cancer is thought to arise from one
13 of the neural crest stem cell derivatives that
14 gives rise to these APUD cells, the various
15 neuroendocrine cells that spread out in certain
16 organs and these cells, termed as Kulchitsky's
17 cells, are thought to be potentially the cell of
18 origin for small cell lung cancer. So, in that way
19 these two tumors do share a common ancestor in the
20 neural crest stem cell.

21 [Slide]

22 Now, if one looks at the staging for
23 neuroblastoma, we see a very distinct set of stages
24 that are clearly related to prognosis. In fact,
25 these stages are probably very directly related to

1 biology as well such that localized tumors, even
2 the partially resected stage 2s, will do quite well
3 with no chemotherapy, indicating that they are a
4 distinct biological subgroup from the more
5 widespread tumors and the more aggressive tumors.

6 There is no counterpart to these in small
7 cell lung cancer. What we see in small cell lung
8 cancer are basically two stages that are defined by
9 the adults, one of which is extensive, widespread
10 disease and the other is more local, regional
11 disease and they do have a prognostic impact. The
12 more localized tumors do significantly better than
13 the more widespread tumors. Those probably
14 correspond to these two stages in neuroblastoma,
15 high risk stage 3 which is a bad biological feature
16 of local, regional tumor and then the more
17 widespread or completely widespread stage 4s. As
18 you will see, this is our major problem in
19 neuroblastoma, the stage 4 patients that present
20 over one year of age.

21 For completeness, another staging
22 component that was initially identified by Chick
23 Coop, Audrey Evans and Dan DiAngelo, the stage 4S
24 tumors, are widespread disease that can
25 spontaneously regress with no therapy at all. That

1 occurs only in infants in neuroblastoma and clearly
2 has no counterpart that we know of in small cell
3 lung cancer.

4 [Slide]

5 If one looks at sites of disease, clearly
6 there are differences in the sites of disease,
7 mainly the primary tumor. The small cell lung
8 cancer presents in the lung, whereas neuroblastoma
9 presents anywhere where there is sympathetic
10 nervous tissue but a very common site of it to
11 present is in the adrenal.

12 However, if one looks at the metastatic
13 sites, there is almost complete overlap.
14 Neuroblastoma and small cell lung cancer both
15 frequently present at diagnosis with bone marrow
16 metastases and that is a common site of recurrence
17 for both of these. They both commonly have liver
18 metastases and whereas small cell lung cancer can
19 present -- and in fact sometimes the initial
20 presenting symptoms, in fact, the first small cell
21 patient I ever saw as a medical student, that is
22 how he presented with a seizure from a CNS
23 metastasis, that then through a chest x-ray showed
24 us that he had a small cell lung cancer. That is
25 not seen in neuroblastoma where CNS metastases at

1 diagnosis are exceedingly rare.

2 However, at relapse, now that we are
3 starting to control the disease, we are,
4 unfortunately, starting to see a significant
5 increase in the number of CNS metastases in these
6 relapse patients. So, there is some degree of
7 overlap in that site of disease as well.

8 [Slide]

9 In neuroblastoma we see a spectrum of
10 differentiation. You can see this in an individual
11 patient if you serially biopsy particularly stage
12 4S patients when they are aggressive. You can see
13 highly undifferentiated and metastatic cells that
14 mature through these differentiated phenotypes with
15 pseudorosettes all the way to a benign
16 ganglioneuroma, which is very reminiscent
17 histologically of a sympathetic ganglion.

18 One does not see this kind of
19 differentiation in small cell lung cancer and so
20 there is clearly a difference between them there.
21 As you will see, therapeutically we have been able
22 to apply this differentiation in neuroblastoma and
23 it probably can't be applied in small cell.

24 [Slide]

25 If one looks at localized disease in

1 neuroblastoma, this is essentially a surgically
2 cured disease and, as you see from these data from
3 the cooperative group, with a fairly good long-term
4 follow-up period, these patients with no
5 chemotherapy are doing quite well. So, this is
6 another clear difference between small cell and
7 neuroblastoma in that localized disease patients do
8 quite well.

9 [Slide]

10 I would like to turn to some of the
11 molecular features, in particular the myc oncogenes
12 which, as you remember, were initially identified
13 by Michael Bishop and Harold Varmus, the v-myc gene
14 being the viral version of the cellular homolog
15 c-myc. Manfred Shrawin, in Michael Bishop's lab,
16 was then able to look at neuroblastomas which were
17 well-known to have some sort of amplified gene
18 because they carried double minutes, and the MYCN
19 gene, which has homologous sequence to c-myc and is
20 found to be amplified in a large proportion of
21 neuroblastomas. Almost half of the high risk
22 patients have amplified c-myc.

23 Then Marion, now working with John Minner,
24 over at NCI Navy, were able to do exactly the same
25 thing. Knowing that there were amplified sequences

1 of myc genes in small cell lung cancer, they were
2 able to fish out another homolog of c-myc, the
3 L-myc gene. So, those are the three myc genes, one
4 being primarily derived from neuroblastoma but, as
5 you will see, that is also amplified in some small
6 cell patients, and one being derived primarily from
7 small cell lung cancer.

8 [Slide]

9 This amplification occurs, as you will
10 see, at the chromosome 2 region where NMYC is
11 located. It is believed that there is an excision
12 of the gene which leads to plasmids that turn into
13 double minute chromosomes and that those can be
14 then integrated back into chromosomes as
15 homogeneous staining regions, but regardless of the
16 cytogenic manifestations, the multiple copies of
17 the gene are seen in about 25 percent of all
18 neuroblastoma primary tumors and, as you will see,
19 that has significant prognostic outcome
20 relationship. This amplification basically
21 provides a large amount of NMYC RNA which then
22 overcomes the short half-life for NMYC and
23 generates a large amount of NMYC protein.

24 [Slide]

25 This shows, from a study that was reported

1 by Marilee Schmidt in JCO in 2000, one of the more
2 dramatic demonstrations of the impact NMYC
3 amplification in neuroblastoma. We are looking
4 here at patients who have stage 4 neuroblastoma
5 that present as infants. Those patients that have
6 no NMYC amplification get relatively modest, not
7 superintensive, chemotherapy and do extremely well
8 whereas, in spite of whatever aggressive therapy
9 you can try to get into these infants, those
10 patients with MYCN amplified disease do extremely
11 poorly.

12 [Slide]

13 In my laboratory we have been spending a
14 lot of time trying to characterize drug resistance
15 mechanisms, and this is some work I wanted to share
16 with you from Nina Kashlava where she has looked at
17 a variety of different neuroblastoma cells lines,
18 and here are just some representative ones
19 established at diagnosis, then some established at
20 PD-IND at progressive disease during ararfrin
21 induction therapy, then the PD-BMT are cell lines
22 that were established at time of progressive
23 disease after myeloablative therapy. Shown on this
24 axis is the amount or resistance of these cells to
25 various agents. The two platinum compounds,

1 carboplatinum and cisplatinum, nafolem, then
2 doxorubicin in red, and finally in yellow
3 etoposide. As you see, we go from diagnosis where
4 there is extreme sensitivity, as you will see and
5 we also see this extreme sensitivity in the
6 patients, as you go through the various stages of
7 therapy, as this therapy gets more intensive those
8 recurrent tumors that we then place in a culture
9 have a sustained, very high level of drug
10 resistance.

11 We looked at a variety of different
12 mechanisms for this and we weren't able to pin
13 anything on it. But, what Nina did was then to
14 examine p53 function and what she found is
15 summarized in the next slide.

16 [Slide]

17 The loss of p53 function, primarily by
18 mutation which is virtually never there -- only two
19 percent of all neuroblastomas as primary tumors
20 have mutation at p53, but in these cell lines that
21 are highly drug resistant there was an incredible
22 correlation with loss of p53 function, again,
23 mostly by mutation. If she knocked out, as you see
24 in the yellow squares here, p53 function by
25 transducing in the 16EC6 protein, then on this axis

1 we see the LC90 for a variety of drugs. The red
2 bars indicate the clinically achievable levels and
3 we go from responsive cell lines that can be killed
4 by clinically achievable levels to, as you see in
5 the yellow symbols, those p53 non-functional lines
6 are virtually never killed by clinically achievable
7 levels of the drug.

8 Now, there are some exceptions with new
9 agents which are p53 independent, but for those
10 agents -- the alkylators, the platinum, etoposide,
11 the agents we commonly use for neuroblastoma -- a
12 loss of p53 function appears to be one of the
13 mechanisms by which drug resistance occurs.

14 [Slide]

15 If we go to the bottom of this table, we
16 see that that can be related back to small cell
17 lung cancer where p53 mutations are present in a
18 high proportion of these. From the literature it
19 is not clear whether these are mutations detected
20 at diagnosis or after chemotherapy. In talking
21 with Dr. Kaye, it was clear that he feels that a
22 number of these tissues were procured at various
23 points in time during therapy so this may be a
24 mixed bag and not just at diagnosis.

25 With neuroblastoma, again, there is a

1 large body of literature showing that essentially
2 if you take it all and do a meta-analysis two
3 percent of the tumors are mutated. We are starting
4 to see from the cell lines in the tumors we are
5 looking at clearly more than 20 percent, we don't
6 know what the exact number is going to be, in the
7 post-chemotherapy neuroblastomas p53 mutations.

8 So, just on that basis alone, one of the
9 things I am going to try and do is draw a very
10 strong parallel between relapse neuroblastoma and
11 small cell lung cancer in terms of its behavior.
12 In fact, the clinical behavior of these diseases is
13 quite identical in that they both do poorly
14 eventually with chemotherapy. Even though there is
15 some response, both relapse neuroblastomas and
16 small cell lung cancer are incurable diseases.

17 There are other parallels that one can see
18 in molecular biological features. MYCN
19 amplification, as we said, occurs in half of the
20 neuroblastomas but it also occurs in small cell
21 lung cancer, with at relapse or at diagnosis.
22 Unlike small cell, we don't see c-myc amplification
23 or L-myc amplification in neuroblastoma but both of
24 those genes can be amplified in small cell as well.

25 Neuroblastoma is an adrenergic tumor and,

1 therefore, secretes catecholamines quite
2 frequently. That is not seen in small cell lung
3 cancer. But other neuroendocrine features,
4 chromogranin expression, PGP9.5 expression, NSE,
5 the leu-7 antigen -- a variety of neuroendocrine
6 features are seen both in neuroblastoma and small
7 cell lung cancer. They appear to have different
8 tumor suppressor loci, however, whereas deletion of
9 3P is the most common deletion seen in small cell,
10 and it is a deletion of the short arm of 1 in
11 neuroblastoma, although there are some P1 deletions
12 that are reported in small cell lung cancer.

13 [Slide]

14 This is a curve showing the CCG data at
15 two periods of time. initially the 1978 to 1985
16 studies in the CCG were stage 4 neuroblastomas
17 presenting over one year of age, and then the data
18 that was obtained in the period from 1986 to 1995.
19 You can see that there is a clear-cut and
20 statistically significant improvement in survival
21 for stage 4 neuroblastomas presenting at greater
22 than one year of age.

23 There are probably two major reasons for
24 this, one of which is the application of very
25 intensive therapy, as I will show you in a moment.

1 The other is the application of
2 differentiation-inducing therapy. This shows you
3 an NMYC amplified neuroblastoma in culture, which
4 is then treated, in the panel on the right, with 10
5 micromole retinoic acid and it shows you the
6 remarkable growth arrest and differentiation that
7 can be achieved with that agent. There is no known
8 parallel to this in small cell lung cancer and we
9 don't know of any differentiation inducers that are
10 effective like this.

11 Going clinically with that, in the CCG-389
12 study we were able to show that the combination of
13 intensive myeloablative therapy, supported by
14 autologous bone marrow transplant, or ABMT,
15 followed by 13 cis-retinoic acid gives the highest
16 survival rate that you can get for this particular
17 form of neuroblastoma, the high risk disease. That
18 is, in fact, what is now being applied essentially
19 worldwide for treating this tumor -- myeloablative
20 therapy followed by a differentiation inducer.
21 Other types of therapies to go along with 13
22 cis-retinoic acid are being tested. For example,
23 monoclonal antibody therapy is being tested in
24 Europe and will soon be tested here, in the U.S.

25 [Slide]

1 Now, if one looks at the response rates to
2 induction chemotherapy for both small cell lung
3 cancer and neuroblastoma, they are identical. Both
4 of these diseases with combination chemotherapy get
5 a response rate of 80-90 percent. There are
6 clearly more CRs that are achieved in
7 neuroblastomas than there are in small cell lung
8 cancer but they both get an almost identical
9 response rate.

10 [Slide]

11 What I find even more striking is to look
12 at the clinically activity of the drugs. Shown in
13 yellow are all those agents that are used as
14 standard parts of therapy, components of standard
15 therapy now for neuroblastoma and small cell lung
16 cancer. You see that those agents are identical.
17 By empirical clinical studies the exact same agents
18 have been shown to be useful in these two diseases.

19 Now, other agents that are used less
20 frequently in these diseases, such as ifosfamide,
21 topotecan and paclitaxel -- we don't know for
22 paclitaxel; certainly we know for ifosfamide and
23 topotecan that they are active in both of these
24 diseases. For melphalin there is not enough data
25 to say whether it is active in small cell lung

1 cancer, presumably it would be. And, 13
2 cis-retinoic acid presumably would not be but we
3 don't have that data.

4 But in spite of those two, there is this
5 enormous overlap and I would like to propose this
6 as one paradigm for trying to look at diseases,
7 disparate diseases. Here we have a lung cancer in
8 adults, caused by smoking, and an embryonal neural
9 system tumor and if you look at the pattern by
10 empirical studies of drugs that have been found to
11 work, they are almost identical. If you take that
12 as a paradigm for trying to apply the Pediatric
13 Rule I think it makes a lot of sense, that if by
14 empirical observation we find that the pattern of
15 agents has been the same perhaps the next agent
16 that is going to be tested, unless it is targeting
17 some specific pathway not known to be in the
18 particular tumor, could be also useful.

19 One can extend this beyond what we are
20 talking about here to diseases such as embryonal
21 carcinoma of the testes where there is a
22 considerable overlap with this pattern as well of
23 the agents being active, and we also know that the
24 same is true in terms of p53 -- embryonal carcinoma
25 of the testes virtually never mutated at diagnosis

1 but at relapse tumors do have p53 mutation. So, I
2 think we can draw a lot of parallels.

3 [Slide]

4 I wanted to end by saying we can go back
5 the other way. These are data from my laboratory
6 looking at fenretinide, a cytotoxic retinoid, in
7 combination with safingol. You can see in these
8 neuroblastomas which include post-BMT relapse
9 neuroblastoma that these cell lines are totally
10 resistant to virtually every agent we can throw at
11 them. And, if we use this combination of
12 fenretinide plus safingol we get this striking
13 multi-log cytotoxicity at dose levels here, at
14 least in tissue culture, that are totally non-toxic
15 for normal myeloprogenitors and fibroblasts. So,
16 we are very interested in developing this therapy.
17 In fact, the NIH is supporting developing it
18 through a grant.

19 [Slide]

20 My colleague has looked at this in small
21 cell lung cancer, and this is one of several lines
22 he has looked at, and he sees exactly the same
23 striking synergy with these agents. So, it may be
24 that agents that are developed in the pediatric
25 community could be then brought back forward to

1 adult diseases, and I think we ought to think about
2 going both ways in this area when we are trying to
3 link diseases.

4 [Slide]

5 So, I would like to end by saying that I
6 think there are substantial similarities between
7 neuroblastoma and small cell lung cancer. These
8 similarities include metastatic sites, the
9 neuroendocrine markers and antigens that are
10 expressed on these tumors; their molecular
11 biological features; their initial response rates
12 to chemotherapy, which I think is very important;
13 and especially their profile of clinically active
14 drugs.

15 Based upon those, I think these
16 similarities suggest that drugs developed for
17 either disease should be strongly considered for
18 clinically testing in the other. Thank you.

19 Discussion

20 DR. SANTANA: Thank you, Pat. We have
21 time now for discussion. I want to get started now
22 myself. The question kind of relates to this
23 analogy that you are proposing between aggressive
24 neuroblastoma and aggressive small cell lung
25 cancer. The question is, yes, there may be many

1 similarities but the similarities may be truly
2 coincidental; may have to do with what ultimately
3 causes cancer in a very simplistic way and totally
4 unrelated to the two diseases independently. But
5 there are also a lot of differences. So, the
6 unifying principle is not quite there because there
7 are as many differences between the two diseases as
8 there are similarities. So, I wanted you to expand
9 a little bit on that and where you think those two
10 cross so that we can then propose when somebody
11 comes to the agency with small cell lung cancer
12 drug development that they consider neuroblastic
13 tumors in that development too. So, do you want to
14 tackle that one? It is a very general question,
15 not very specific.

16 DR. REYNOLDS: What I am trying to do here
17 is to show that certainly there are differences but
18 there are also similarities and the real question
19 at hand, as I understand it from the FDA's
20 consideration of the Pediatric Rule is whether or
21 not there is enough evidence to link an adult
22 cancer to a pediatric cancer to indicate that a
23 study is warranted. And, I believe that based upon
24 not only the biological features, even you consider
25 that there are differences between them, but

1 especially based upon the history that we find by
2 empirical drug development in small cell lung
3 cancer and neuroblastoma, given that so many of
4 these agents have been shown to be active for both
5 of these tumors, that would be, at least from my
6 perspective, strongly suggestive that a study
7 should at least be considered in neuroblastoma for
8 an agent that is being brought forth for as an
9 indication for small cell also.

10 DR. SANTANA: Jerry?

11 DR. FINKLESTEIN: Pat, if you did the same
12 kind of comparison with, say, malignant melanoma
13 what would you show, and have you done it? I say
14 that because that is another neural crest cell
15 tumor which many of us have grown up thinking in
16 terms of neuroblastoma. What do you think you
17 would find?

18 DR. REYNOLDS: Well, I haven't done that
19 comparison at the depth I would like to, to answer
20 that question but there are certainly some
21 similarities. They are both neural crest cell
22 derived. They share some common antigens. In fact
23 the NTGD2 antibody which was developed for
24 neuroblastoma therapy is being tested in melanoma
25 and in small cell as well. So, there is clearly

1 some overlap there. The striking similarities in
2 terms of similar histology is there; metastatic
3 pattern is not there, nor is the response rate or
4 identical profile of drugs. But I think there is
5 overlap there and it certainly should be looked at
6 carefully.

7 DR. LINK: You had me going until the last
8 business about this comparison of the drug
9 sensitivity profile as a way of relating the two
10 because, you know, everything in pediatrics is
11 sensitive to dactinomycin, cyclophosphamide and
12 Adriamycin. So, if you took those three drugs and
13 said that Ewing's is like rhabdomyosarcoma because
14 they both respond to those three drugs you would
15 sort of set back all of this splitting that we have
16 been doing in defining a molecular underpinning for
17 the specificities of the cancer. In fact, there
18 are those people who say small round cell tumor --
19 just give them cyclophosphamide and Adriamycin and
20 it should go away, like our pathologists at my
21 institution when they refuse to do these molecular
22 tests.

23 [Laughter]

24 So, I think you have a very cogent
25 argument. And then the last slide with the

1 fenretinide -- but I think we have to be very
2 careful about sort of putting on record that
3 anything that responds to three drugs is likely to
4 be the same because ultimately those are the only
5 three drugs that are useful for most adult tumors,
6 and platinum I guess. So, you are lumping a lot of
7 things where we would be going both ways. That is
8 my fear.

9 DR. REYNOLDS: I agree with you totally,
10 Mike. My point with this was not that we could
11 lump small cell lung cancer in with neuroblastoma
12 and do trials. Obviously, you can't do
13 myeloablative therapy in these 16-year old patients
14 and there is a whole variety of reasons why you
15 can't treat them the same. What I am suggesting
16 is, is an agent that is active in one likely to be
17 active in another? That is the real question that
18 we are getting at for the purposes of this
19 committee. I think based upon those data, there is
20 a strong history that would suggest that if an
21 agent was tested in one and was active, it was
22 likely to be active in the other.

23 DR. COHN: I was just going to say that I
24 think, again, we have to think about this. It is a
25 neuroendocrine tumor much like a melanoma is a

1 neuroendocrine tumor and there are certainly some
2 antigens that are similar; there are some
3 amplifications, some genes that are similar; and
4 there are certainly presumably some biologic
5 pathways in terms of cell growth and development
6 that are probably similar. I think, once again, we
7 need to take into account Steve's slide. Rather
8 than trying to lump small cell and neuroblastoma
9 together, I think it is much more important to say
10 what is the drug? What is the pathway targeting?
11 Is the pathway prevalent in both small cell lung
12 cancer and neuroblastoma? If the answer is yes,
13 for example, GD2 is an antigen and you could
14 potentially use that particular therapy in both
15 diseases. Then, you know, I think it makes sense.
16 But I agree that to just say, you know, that a drug
17 that destroys DNA and basically kills cells the way
18 chemotherapy does to be sensitive in both probably
19 isn't a rational approach.

20 DR. ELIAS: Just a comment because it is a
21 struggle I think. The devil is in the details, so
22 to speak, in terms of when we try to define a
23 treatment according to its biologically targeted
24 activity. If we take the example, for example, of
25 Herceptin in breast cancer and we say, okay, now

1 with FISH we think we have a negative predictive
2 factor in breast only, if that is not amplified
3 then Herceptin doesn't seem to work. If it is
4 amplified, it does work. However, when we think
5 about it working, it really only works, let's say,
6 20 percent of the time, at least by itself.

7 So, the point really is, number one,
8 should we spend an enormous amount of time trying
9 to validate the target by looking at the assay
10 used? Number two, it is clear that even when the
11 target is validated the results are very
12 spectacularly heterogeneous, and we don't
13 understand why a Her2 overamplified breast cancer
14 doesn't response. The third, it is also being
15 defined specifically for Herceptin and it is fairly
16 clear -- well, no, it is not fairly clear but it,
17 hopefully, will become clear that if you use a
18 different targeting method or a different molecule
19 you might, in fact, get a completely different
20 answer in terms of what is important biologically
21 in that pathway.

22 So, yes in small cell we have GD2, we have
23 GD3, we have a number of overlaps particularly in
24 neuroendocrine type pathogens that are relevant in
25 neuroblastoma and melanoma, for that matter -- I

1 mean, we can go and look at a lot of similarities
2 and if we have a specific target it might be
3 relevant but I think it comes back to what Howard
4 said, that we have to be absolutely sure that these
5 are meaningful in that disease and that they are
6 going to have a biological effect. And, I think
7 that is where we fall apart a little bit. I don't
8 think we know that.

9 DR. SMITH: I have a biological question
10 for Dr. Kaye. You know, Pat shared his data with
11 the p53 and how that decreases the
12 chemosensitivity, yet, in this very chemoresponsive
13 or initially chemoresponsive cancer there is a high
14 percentage of p53 mutations and not in
15 neuroblastoma in response to the same drug. Is
16 there any explanation of how you can have such a
17 high percent of p53 mutations and yet be so
18 chemoresponsive, as opposed to the situation in
19 neuroblastoma where once those mutations appear you
20 lose much of your chemosensitivity?

21 DR. KAYE: Small cell lung cancer is a
22 really tough disease for oncologic research because
23 it tends not to be a surgical disease. It is
24 almost never a surgical disease. So, there is
25 almost no primary material to deal with, and a lot

1 of the biopsies are on needle aspirates or small
2 bronchoscopic biopsies. So, I am not so certain
3 that how much of the mutational data for the tumor
4 was done pre-therapy and you are going to be skewed
5 a little bit more for more advanced stage.

6 There is an interesting point with myc
7 amplification. I showed a very low incidence of
8 myc amplification in lung cancer. Earlier data
9 showed a much higher incidence. There is a
10 question as to why you don't see as much myc
11 amplification now as you did earlier on. There
12 have been a few studies that tried to say -- again,
13 that data was often done after patients had been
14 subjected to chemotherapy -- so, there was an
15 argument, and I am not sure how tenable it is, that
16 cytoxin-Adriamycin, which was the most common
17 regimen that was used for small cell lung cancer
18 earlier, might be pressuring these cells to undergo
19 myc amplification while cisplatin-etoposide might
20 not have the same genotoxic stress and that might
21 be a reason why. But, again, a lot of this data is
22 done post-treatment. So, it is plausible that p53
23 is not targeted early.

24 The counter thing is that, again, if you
25 target especially the RB gene, those cells with

1 wild type p53 undergo apoptosis almost immediately.
2 So, it is impossible to find any sample or cell
3 line that has a mutant RB relating to wild type p53
4 function. So, I think there is no answer to that
5 question.

6 Questions to the Committee

7 DR. SANTANA: Any other comments? If not,
8 I want to go ahead and start with the questions so
9 we can remain on time. As I did earlier this
10 morning, I want to take a first pass proposal to
11 answer the first question.

12 This relates to what general principles
13 should be used -- I am going to change the
14 question, not "could" but "should" be used to
15 relate malignancies in adults to neuroendocrine
16 malignancies in children?

17 I would propose the following, clearly, as
18 has been demonstrated well by Pat and Dr. Kaye
19 today, there are many similarities between the
20 general spectrum of neuroendocrine malignancies in
21 adults and in children, and specifically maybe with
22 the two examples that were shown, small cell lung
23 cancer and neuroblastoma. But, there are also many
24 differences. I am not comfortable stating that the
25 similarities outweigh the differences so that I

1 think we should take a unified approach of lumping
2 these things together when it comes to interpreting
3 the regulations, with the exception that if a
4 product is coming forth, as has been alluded to,
5 which is specifically indicated for a biologic
6 target and that biologic target has been
7 demonstrated to be important and relevant both in
8 small cell lung cancer and also demonstrated
9 preclinical and biologically in neuroblastoma that
10 in that case there should be a link and you should
11 request pediatric studies but only in the context
12 of where there has been a predefined common
13 element, a targeted therapy that is biologically
14 relevant and suggests that it may be effective
15 would I consider that the two diseases be unified
16 in terms of the regulation. That would be my
17 answer to this question. I don't know if the rest
18 of the committee agrees so please speak up.

19 DR. PAZDUR: Would you advocate that that
20 target should be actually measured in a
21 subpopulation?

22 DR. SANTANA: Yes.

23 DR. PAZDUR: Say, if somebody was
24 developing a drug for lung cancer but they were
25 targeting and measuring a specific enzyme that they

1 were inhibiting, and it was only going to be used
2 on that specific population so it really targeted
3 --

4 DR. SANTANA: Yes.

5 DR. PAZDUR: -- rather than a more general
6 -- you know, this may inhibit enzyme, cure,
7 whatever.

8 DR. SANTANA: Correct. I think it needs
9 to be defined very precisely and targeted very
10 precisely. Mike?

11 DR. LINK: Just more of a generic
12 question, and I am not sure it is directed to you
13 but do you really want to have separate principles
14 for sarcomas and separate on -- I am a little
15 nervous that you had kind of a nice proposal for
16 sarcomas -- at least I thought it was nice -- and
17 now you are kind of dancing around a little thing
18 here to try to accommodate a very different
19 approach. Maybe we should try to go back to the
20 sarcoma one and amend it a little bit to looking at
21 a pathway that might be targeted, which wasn't
22 included in the sarcoma thing, rather than trying
23 to make a totally different thing here for a
24 different class of tumors.

25 DR. SANTANA: Mike, I will give you my own

1 bias. My own bias is that in sarcomas the diseases
2 clinically, pathologically, etc., are very similar
3 and the differences are minor, whereas in this
4 example that we are being given now I think the
5 similarities and differences are very obvious --

6 DR. LINK: I agree totally with what you
7 said --

8 DR. SANTANA: -- so, I think I want to
9 propose --

10 DR. LINK: -- the diseases are the same or
11 the pathway is the same, not that you have a
12 principle for sarcomas and a different principle
13 for neuroendocrine tumors and now we are going to
14 have brain tumors and we are going to have a third
15 different principle there -- you know, kids' brains
16 are fully developed or brains are not fully
17 developed. It seems more rational to have a
18 unifying principle which is either a targeted
19 pathway or that the tumors are identical on a
20 genetic --

21 DR. PAZDUR: I think there could be
22 differences here. I think an uncomfortable feeling
23 that we are having here in dealing with small cell
24 lung cancer versus neuroblastoma is that even
25 though if somebody had a similar mechanism here