DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC SUBCOMMITTEE

OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

Thursday, October 17, 2002

8:25 a.m.

Advisors and Consultants Staff Conference Room
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

Victor M. Santana, M.D., Chair
Thomas H. Perez, M.P.H. Executive Secretary

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Jody L. Pelusi, F.N.P., Ph.D.
Donna Przepiorka, M.D., Ph.D.
Gregory H. Reaman, M.D.

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Peter Adamson, M.D.
Alice Ettinger, R.N.
Jerry Finklestein, M.D.
Ruth Hoffman
Robert Nelson, M.D., Ph.D.
Patrick C. Reynolds, M.D.
Victor Santana, M.D.
Susan Weiner, Ph.D.

GUEST SPEAKERS (NON-VOTING)
Barry Anderson, M.D., Ph.D.
Susan Blaney, M.D.
Joachim Boos, M.D.
Peter Houghton, M.D.
Eric Kodish, M.D.
Bruce Morland, M.D.
Dave Poplack, M.D.
Edward Sausville, M.D.
Malcolm Smith, M.D.

INDUSTRY GUESTS (NON-VOTING)
David Emanuel, M.D.
Anne Hagey, M.D.
Judith Ochs, M.D.
Wayne Rackoff, M.D. (by telephone)
Steven Weitman, M.D.

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

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Introductions

DR. SANTANA: Good morning and welcome. This is one of a series of meetings that the Pediatric Oncology Subcommittee of the Oncology Drugs Advisory Committee for the FDA has had. We began our work, I believe in September of 2000 and have had a number of meetings advising the agency of issues related to pediatric oncology.

Dr. Hirschfeld later on in the morning will actually describe for us the charge that we have before us today.

With that, we will get the meeting started. I do want everybody to introduce themselves. Please use the microphone as there are minutes that are generated from this discussion, so please state your name, your affiliation.

You have to hit the little talk button on the righthand side of your speaker. If it is turning red, you are being recorded, so be careful what you say among yourself. It will be there for posterity.

Can we start with Joachim over here in corner, please.

DR. BOOS: My name is Joachim Boos. I am

coming from Germany, from the University of M
nster
and from the German Pediatric Oncology Society.

DR. BLANEY: I am Susan Blaney from Texas Children's Cancer Center, Baylor College of Medicine.

DR. HOUGHTON: Peter Houghton, St. Jude Children's Research Hospital.

DR. POPLACK: David Poplack, Texas Children's Cancer Center, Baylor College of Medicine.

DR. MORLAND: Bruce Morland, pediatric oncologist from Birmingham Children's Hospital in the UK, representing the United Kingdom Children's Cancer Study Group, New Agents.

MS. HOFFMAN: Ruth Hoffman, Candlelighters Children's Cancer Foundation.

DR. NELSON: Robert Nelson, Children's Hospital, Philadelphia.

DR. REYNOLDS: Pat Reynolds, Children's Hospital, Los Angeles.

DR. FINKLESTEIN: Jerry Finklestein, UCLA, Long Beach, and the American Academy of Pediatrics.

MS. ETTINGER: Alice Ettinger, St. Peters University Hospital and the Association of Pediatric Oncology Nurses.

DR. ADAMSON: Peter Adamson, Children's Hospital of Philadelphia, representing the Children's Oncology Group Developmental Therapeutics Program.

MR. PEREZ: Tom Perez, Executive Secretary to this meeting.

DR. SANTANA: Victor Santana from St. Jude Children's Research Hospital in Memphis.

DR. PELUSI: Jody Pelusi, oncology nurse practitioner, and I am sitting as the consumer rep.

DR. PRZEPIORKA: Donna Przepiorka, University of Tennessee Cancer Institute from ODAC.

DR. REAMAN: Greg Reaman, Chairman of the Children's Oncology Group in Children's Hospital and George Washington University here in D.C.

DR. WEINER: I am Susan Weiner. I am from the Children's Cause, and I am a patient rep.

DR, HIRSCHFELD: Steven Hirschfeld, U.S. Public Health Service, Food and Drug Administration, the Division of Oncology Drug Products and the Division of Pediatrics.

DR. GOOTENBERG: Joe Gootenberg, U.S. Food and Drug Administration, Center for Biologics, Oncology.

DR. PAZDUR: Richard Pazdur, Division of

Oncology Drug Products, Food and Drug Administration.

DR. SMITH: Malcolm Smith, Cancer Therapy Evaluation Program, National Cancer Institute.

DR. SAUSVILLE: Ed Sausville, Developmental Therapeutics Program, National Cancer Institute.

DR. ANDERSON: Barry Anderson, Cancer Therapy Evaluation Program, National Cancer Institute.

DR. OCHS: Judith Ochs, AstraZeneca Pharmaceuticals.

DR. HAGEY: Anne Hagey, Abbott Pharmaceuticals.

DR. WEITMAN: Steve Weitman, Ilex Oncology.

DR. SANTANA: Anybody on the phone that wants to introduce themselves?

DR. RACKOFF: This is Wayne Rackoff with Johnson & Johnson.

DR. SANTANA: Thank you, Wayne.

I am going to pass on the microphone to Richard Pazdur, the Director of the Oncology Drugs Program for a brief welcome.

Welcome

DR. PAZDUR: I would just like to thank you on behalf of the Center for Drug Evaluation and Research and the FDA for your attendance at this meeting.

It also gives me great pleasure to introduce one of our new members basically to the Center for Drug Evaluation, and that is Dr. Shirley Murphy, who assumed the position of Director of the Division of Pre-Pediatric Drug Development, whose mandate is basically to implement the Best Pharmaceuticals in Children's Act.

Dr. Murphy has had a long academic career. She was Chair of the Department of Pediatrics at the University of New Mexico, is a renowned pediatric immunologist and pulmonologist, and before joining the FDA spent four years in industry.

Shirley, do you have any words?

DR. MURPHY: I am just very happy to be here. Actually, Jerry Finklestein was my mentor. He was the faculty person when I was a resident, and this is the first time I have seen him in 20 years, and he looks--or I think it is more than 20, Jerry--but he looks better than ever.

When I was a resident, I took care of his

oncology patients when he would go on vacation, so it is very happy to come full circle and be part of the children's oncology community. I look forward, through the legislation that we have together, we are really mandated to bring oncology medications forward for children and to make sure children aren't left out of the loop.

So, I look forward to working with all of you.

DR. PAZDUR: Thank you, Shirley, and we honestly look forward within the center and also within this committee to work with you. Thanks.

DR. SANTANA: Thanks to both of you, and we also do welcome your involvement and helping us figure all these issues out.

I think we have an administrative issue, which is the conflict of interest, so I will have Mr. Perez read that document, please.

Conflict of Interest

MR. PEREZ: Thank you.

The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The topics of today's meeting are issues of broad applicability. Unlike issues before our committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All special government employees and federal guests have been screened for their financial interests as they may apply to the general topics at hand.

Because they have reported interests in pharmaceutical companies, the Food and Drug Administration has granted general matters waivers to the following special government employees which permits them to participate in today's discussions: Dr. Peter Adamson, Dr. Jerry Finklestein, Dr. Robert Nelson, Dr. Jody Pelusi, Dr. Donna Przepiorka, Dr. Greg Reaman, Dr. Victor Santana, Dr. Susan Weiner, and Ms. Alice Ettinger.

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

Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to

each member, consultant, and guest.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before this subcommittee, these potential conflicts are mitigated.

We would also like to note that Dr. Anne Hagey, Dr. David Emanuel, Dr. Judith Ochs, Dr. Wayne Rackoff, and Dr. Steven Weitman are participating in today's meeting as non-voting industry guests. As such, they have not been screened for conflicts of interest.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

That concludes the conflict of interest statement.

I would like to acknowledge that on the

phone we have one guest participant, Dr. Wayne Rackoff from Johnson & Johnson. Also, on the phone, if not now, maybe later, are representatives of the European Medicinal Evaluation Agency. They have a number of individuals that will be listening in, not participating, in today's meeting.

The EMEA has been intimately involved with the FDA in the development of guidances on many topics, areas that are of mutual interest to both agencies. Today's topic is one of these areas and therefore they have been invited to listen in to the meeting's discussions.

Thank you.

DR. SANTANA: Thanks, Tom.

Does anybody have any conflicts of interest that they wish to further disclose?

[No response.]

DR. SANTANA: Thank you.

I am going to now invite Steve Hirschfeld from the Division of Oncology Products to give the charge to the committee and overview of the issue at hand today.

Steve.

Charge to Committee

DR. HIRSCHFELD: Good morning, everyone,

and welcome to this meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee. This is our first meeting under the new mandate from the Best Pharmaceuticals for Children Act, and this committee has been written into law, which I think is a recognition of the importance of the work of this committee.

I would like to thank some people. To begin with, I want to thank Captain Thomas Perez of the U.S. Public Health Service for picking up the administrative responsibilities for this committee, which have been complex and diverse, and for coordinating the many, many tasks which were required to put this meeting together. I think he has done it not only successfully, but in an exemplary way, so thank you, Captain Perez.

I want to thank also Dr. Richard Pazdur, who has been involved from the inception of this committee and has been not only supportive, but a participant in every one of the meetings.

There are some other people, too many in fact to recite by name, but I wanted to note that we have on our panel today two people who have at great inconvenience, but nevertheless with overwhelming enthusiasm, come great distances to be

here.

That is Professor Joachim Boos from the University of Mnster and Professor Bruce Morland from Birmingham Children's Hospital, so thank you both for making that long transatlantic trip and coming here.

I also want to acknowledge the participation of our colleagues from the EMEA and then a special acknowledgment because so many people, not only in this room, but on this very panel, have been under the tutelage over the years of one of the guiding lights I find of pediatric oncology, who has been not only a supporter but a participant and a contributor to the deliberations of this committee, and that is Dr. David Poplack, so thank you for your participation, too.

[Slide.]

This committee first met in September 2000 with a charge of attempting to put a framework on an interpretation of the Pediatric Rule. The Pediatric Rule stated that if a product was under review for an indication that was found in adults, that there was a mandate to develop that product for children.

In oncology, this is particularly

challenging because depending upon how one looks at classifications, there are over 150 cancers, and we, as pediatric oncologists, have been always telling the world that children are different and pediatric tumors are different, but as we have increased our understanding of the biology of tumors, we see that it was, to paraphrase Walter Pater in his Essays on the Renaissance, it was only the limitations of the eye which made us think that some things were the same or some things were different.

As new techniques have evolved, we have attempted to incorporate that thinking into our deliberations. So, in September 2000, we had a meeting of the discussion of methods that may be used to describe and link tumor types.

Then, in April 2001, we focused that discussion on hematologic tumors, and in June 2001, we discussed solid tumors and central nervous system malignancies.

These discussions led to recommendations on how one might approach, both in general principles and with some specific examples, of linking various tumors on a variety of bases. One of the maxims that my pathologist colleagues always

tell me is that there are three things that are certain in life - taxes, death, and classification systems will change.

So, we wanted to have a flexible approach that would allow us to continue to interpret the classification system, so that we could be sure that if it was possible within our scope to enhance product development for children with cancer, we would have that opportunity.

We had tried to apply some of these at a meeting in November 2001 where we discussed study designs and the general principles involved in how we might extrapolate information or borrow data as the case may be, and that will be one of the themes which we will talk about today in our meeting October 2002, what data may we borrow, what data should we look at in terms of making determinations of when pediatric studies should be initiated in children with cancer in a drug development program.

[Slide.]

There is a formal statement regarding pediatric clinical studies which was promulgated from--and several people in this room and on the telephone have worked on it--an efficacy topic called E-11 from the International Conference on

Harmonization.

The premises of that document are that pediatric patients should be given medicines that have been properly evaluated for their use in the intended population, that product development programs should include pediatric studies when pediatric use is anticipated, that pediatric development should not delay adult studies nor adult availability, and lastly, and I think importantly, that shared responsibility among companies, regulatory authorities, health professionals, and society as a whole.

This committee represents all of those constituencies, and we will together share that responsibility and hope that we could make progress.

[Slide.]

The document addresses when pediatric clinical studies should be initiated in two sections. One section is addressing when diseases predominantly or exclusively affecting pediatric patients are under study, and the recommendation is that the entire development program will be conducted in the pediatric population except for initial safety and tolerability data, which will

usually be obtained in adults.

The "usually be" is an interpretive phase which perhaps we can discuss during the course of this conference.

[Slide.]

The other circumstance, which may be more applicable to the pediatric malignancies that we are focused on, is when serious or life-threatening diseases, which occur in both adults and pediatric patients, for which there are currently no or limited therapeutic options.

Then, the medicinal product development should begin early in the pediatric population, following assessment of initial safety data and reasonable evidence of potential benefit.

These recommendations were reached by international consensus among the Japanese, the Europeans, and the Americans, and although several people in this room and others have worked on this, we all recognize that these were in effect interim statements.

They were worded in such a way that they could be interpreted in the various regions and at various times, give us a great deal of flexibility.

[Slide.]

What we would like to do today is ask the question: What information is necessary to consider exposing children with cancer to an investigational agent, or to paraphrase, what should the evidence burden be?

There is a fairly well known routine from a review called Beyond the Fringe, that the late Peter Cook and the late Dudley Moore did where they interviewed, in their impersonations, Bertrand Russell.

They were asking him whether he wanted apples, and there were many permutations on trying to get an answer out. Included in those was "could" or "should" or "must," so in order to clarify, I think we consider all these possibilities, but the encompassing phrase that I would want to recommend in the accompanied principle is what should be necessary to consider exposing children with cancer to an investigational agent.

So, best of luck and we will eagerly await your deliberations.

Thank you.

DR. SANTANA: Thanks, Steve.

I think we are going to have a session after the initial presentations for comments and

discussion, so if anybody has any comments or further questions to Steve, we could come back to him then.

I want to start the official presentations by inviting Dr. Peter Houghton to give us the initial talk that hopefully will lead to a discussion of how we can use preclinical models to help us, guide us more appropriately in trying to deal with some of these issues.

DR. HIRSCHFELD: While we are working on the audiovisual adjustments, I did want to also have a special acknowledgment for the outstanding job that Victor Santana has done as chair of this committee. He has had multiple responsibilities, and yet has always found time to put, not only full effort in preparing for these meetings, but has sometimes done double duty as a presenter and a discussant and a chair, and has managed to have our meetings run exceptionally well and concluding all time.

So, thank you, Victor.

DR. SANTANA: Thanks, Steve. In spite of all that, I still have a job at St. Jude.

Preclinical Models: What Can They Tell Us?

Peter Houghton, Ph.D.

DR. HOUGHTON: It is particularly a pleasure to be here this morning as I am playing hooky from the Study Section in another part of Washington.

[Slide.]

Victor has asked me to talk about preclinical models and what they can tell us, in particular, how can we develop drugs in a rational way for treatment of children with cancer even in the absence of some adult data.

I am going to show you some of the work we have done over the years that suggest that there are preclinical models that may be quite predictive of therapeutic utility of some drugs.

Obviously, no model is perfect, but I think if we use these models reasonably intelligently, they can be quite informative and guide us in both identification of drugs that might be useful in children and how perhaps to best use them in the clinical situation.

[Slide.]

About 20-plus years ago, we started to think about drug development and how drug development for childhood cancers has to be somewhat different because of the limitations and

restrictions that are imposed upon developing drugs for children in relatively rare diseases.

It is clear that virtually no drugs are being developed specifically to treat childhood cancers and particularly solid tumors, so our aim was to develop and validate tumor models to potentially identify important new drugs.

Then, in terms of Phase I testing, how do the Phase I trials really help us to prioritize drugs for Phase II evaluation, and again to develop models that might help develop a process allowing a more rational prioritization.

If we look at the Phase II component of pediatric clinical trials, we can ask whether those trials really reveal any insight as to whether a drug succeeds or fails, and to try and develop models that might help us to understand the success or failure of clinical trials.

[Slide.]

So, the models that we started developing in the early '70s and then with respect to pediatric cancers, when I went to St. Jude in the late '70s, human cancers grown in immune-deficient animals, immune-deprived or congenitally athymic or SCID mice.

These models have been developed by many groups around the world, essentially, now I think we have encompassed most of the models of various childhood cancers, solid tumors, and also there are groups that have models now of acute lymphocytic leukemia from childhood both at the diagnosis and relapse stage.

[Slide.]

When we look at these types of models, we have to think about how to validate them, and in the premolecular characterization era, one of the ways of doing this was to ask whether the models respond qualitatively and quantitatively to drugs known to be active in the respective clinical disease.

So, we can ask if a diagnosis model of rhabdomyosarcoma, for example, whether it is highly sensitive to the drugs that are active in the clinic, and clearly, that is the case.

We can ask whether tumors developed from children that relapse from therapy are significantly less responsive to those drugs in the mouse, and that clearly is the case, and that tells us that it is not just a consequence of transplanting a human tumor into a mouse that

dictates the response.

Then, we can ask whether the models prospectively identify effective agents. We started to look at this in the mid-'80s with Mark Horowitz and Andy Green at St. Jude, and demonstrated that these models could be quite useful in a prospective mode.

So, we look at retrospective data where we look at the drugs that are shown to be active in the clinics, vincristine, cytoxan, dactinomycin, adriamycin, the first three being sort of standard therapy for rhabdomyosarcomas, we can see that in the panel of xenografts, we get a fairly high response rate to vincristine, the lowest response rate to dactinomycin.

On the right side of the presentation, you see the reported clinical response rates to single agents, so this is pretty historic data, and may not be currently applicable to the way these drugs are given at the present time, but at least there is an interesting correlation between the activity in the model systems, and the model systems clearly show activity of drugs that are known to be active if you use the criteria in the model system that is used in the clinic.

We are not particularly interested in growth inhibition, we are interested in tumor regressions and complete regressions as being objective responses in the mouse.

If we look at the model systems in a prospective mode, in the mid-'80s, we identified melphalan, as I mentioned, with Mark Horowitz and Andy Green, and showed that in the model systems, melphalan, a bifunctional alkylating agent, is extremely active in these models, and clinically, at St. Jude, it was shown to be effective in around 80 percent of children at diagnosis with Stage 4 rhabdomyosarcomas in an upfront window trial.

More recently we have looked at topotecan. The response rate in the xenografts is around 70 percent, and has clear activity in clinical rhabdomyosarcoma, interestingly, with a higher response rate in the alveolar subtype rhabdomyosarcomas, which is the predominant model that we use in the preclinical setting.

[Slide.]

Turning to another model which we have developed quite recently is models of Wilms' tumor. We are trying to develop a model of diffuse anaplastic Wilms' tumor, which is very rare, but is

chemo-refractory and has a poor prognosis, but to do this, we have to establish a very large number of Wilms' tumors, and most of them have been of favorable histology shown from WT1 through WT10.

These tumors are exquisitely sensitive to vincristine. The 6+ on these graphs is complete regression without growth during a 12-week period of observation. Similarly, most of these tumors show objective responses either in PRs or CRs to cytoxan in the model system, again very consistent with the activity of these drugs in Wilms' tumor of favorable histology.

In the bottom line SKNEP, which is a diffuse anaplastic, is much less sensitive to vincristine although it retains sensitivity to cytoxan. So, we produced this model to see if we can identify prospectively drugs that might be of value in relapsed Wilms' tumor and the camptothecin agent, topoisomerase I, topotecan, they are exquisitely sensitive to this agent, and this has been the subject of a Phase I trial with Jeff Dome at St. Jude, and will subsequently be put into a national trial based on some rather promising results even in the Phase I trials.

[Slide.]

So, the other aspect is the more modern characterization of these tumors, and that is to look at them in terms of gene expression and proteomics, and the Wilms' tumors have a very high level of expression in certain kinesians, much higher than any other tumor that has been identified by the Glaxo/Smith/Kline group.

Consequently, we are working with GSK now to see if a particular inhibitor will have significant activity against Wilms' tumors, perhaps moving us into more of the molecular realm of drug development.

[Slide.]

So, where do xenograft models fit? We believe they can be useful for identification of novel agents, both classical cytotoxic agents and those that work through defined molecular targets.

We believe we can identify drugs that have very broad spectrum activity both in a wide range of pediatric tumor types when grown in animals. We can identify drugs that show a lack of cross-resistance with currently available therapy.

We believe that the model systems may be helpful in optimizing schedules of administration and will allow us to develop relationships between

tumor response and the systemic exposure of these drugs, and I am going to deal with these last two points in a little bit more detail.

[Slide.]

These are examples of tumor growth and the schedule dependency of the camptothecin agent irinotecan CPT level. Shown on the left panel is the growth of individual tumors in mice, in SCID mice, without treatment.

In the center panel, we are looking at the effect of CPT-11 given for five days with cycles repeated every 21 days over the first eight weeks.

In the right panel, the drug is given over 10 days.

What is important to note is the total dose per week and total dose over the entire course of therapy between the two groups is identical, so lower doses for a longer period of time are clearly more effective than are short, more intense courses. This applies to all the camptothecin agents we have looked at so far.

[Slide.]

At least initial preliminary data largely from Phase I trials suggest that there may be some benefit in going to longer dosing schedules. At

the top is shown available clinical data for topotecan, and at the bottom is shown irinotecan data.

One can see that with a daily times 5, we are seeing even in Phase I some activity around 8 percent, but the two trials that have looked at the protracted schedules of 5 days times 2 are showing considerably higher response rates.

Similarly, if we look at the bottom panel, the two studies that are published using daily times 5 times 2 schedule are clearly giving response rates that are higher than this obtained for the daily times 5.

This is Phase I data, and obviously, it would be nice to do a randomized study in Phase II, but I think the animal data is very compelling. The protracted scheduling of these drugs, which are after all very specific cell cycle dependent killing agents that work only in S-phase during DNA replication, that a protracted schedule of administration makes a lot of sense based on the mechanism of action of this class of agent.

[Slide.]

So, we have, rather than using mouse maximum tolerated doses, we have tried to develop

relationships between response and drug systemic exposure.

[Slide.]

So, we have taken tumors from children, grown them in a variety of mice, and then we can look at questions of dosing, schedules of administration, and relate this to the pattern, pharmacokinetic pattern in terms of systemic exposure and AUC.

Then, we have taken this information and have designed clinical trials that as closely as possible paralleled the results we have obtained in the animals, perhaps to give optimal dosing of these drugs.

So, this allows us to make a comparison of the systemic exposure, the AUC, at a maximum tolerated dose in patients, with the AUC causing tumor regressions in the model systems.

[Slide.]

Retrospectively, we can look at data that we have generated over the last, say, 10 years, and look at a group of drugs that really have not had any activity in the clinic, yet, have had activity in the model systems, or alternatively, have had activity in model systems and have activity in the

clinical situation.

What I have done here is to show you the relative tolerance of the mouse relative to human, AUC, the systemic exposure of a drug at a maximum tolerated dose in the mouse divided by AUC at the MTD in the human.

You can see for DMP-840, there is about a 15- to 20-fold greater tolerance in the mouse than there is in patients. For carzelesin, it is around 80-fold difference.

On the other hand, on the right column, if we look at the effective dose range, so if we are looking for objective responses as a function of decrease from the MTD, the maximum tolerated dose in the mouse, we see that most of these drugs have a very limited range with effective dosage, so carzelesin, for example, we achieve 80 times greater systemic exposure in the mouse than human, and yet, the effective dose range from the MTD in the mouse is less than 2, so if we divide the dose from the MTD by half, we still lose any objective regressions in model systems.

On the other hand, we take a drug such as melphalan, where there is a positive activity in the clinic and in the model systems, we see that

the AUCs are essentially identical in mouse and human, the dose effective range is 3- to 4-fold, and we see activity in the clinic.

For a drug such as irinotecan, which is really a very exceptional drug, we see that the mouse is about 16-fold more tolerant to the active metabolite SN-38. The dose effective range of this drug is around 100, the reason for that, we have at this point no idea.

[Slide.]

On the other hand, we can take a drug that is currently in Phase I and potentially could go into Phase II, MGI-114, and we see that the maximum tolerated dose, we see dramatic activity in 14 out of the 16 tumors. Anything that is a 4+ on this table is an objective regression 50 percent, 5+ is a complete response, 6+ is complete response without regrowth during a 12-week period of observation.

One can see dramatic activity at the MTD in the mouse, but if we reduce that dose by 4- to 5-fold, we see that, in reality, there is only one objective response out of 14 tumors that have been evaluated.

The problem is even at this dose, we are

still 10-fold above the systemic exposure that can be achieved in children. So, this would be a drug that we would say would have a low priority to go forward in a Phase II trial.

[Slide.]

So, with respect to neuroblastoma, we have made one preclinical prediction. Using the topotecan scheduling of daily times 5 times 2, so it is Monday through Friday, Monday through Friday in the animals because we don't treat them at the weekends.

Preclinically, we saw activity, objective responses in 4 out of 6 tumors at a systemic exposure of 100 ng.hr/ml topotecan lactone, which is the active form.

So, we conducted a targeted Phase II trial under the leadership of Victor Santana at St. Jude to target the exposure to 100 ng.hr/ml plus or minus 20 percent. In clinical Stage IV Neuroblastoma, the responses of that trial are 16 out of 28 partial responses or around 57 percent, suggesting that if we translate accurately will be doing the animals, then, there is a good correlation with clinical activity.

[Slide.]

So, where do xenograft models fit in drug development for childhood cancer? It really would be nice to include pediatric tumor models in the early stages in NCI screening or industry or academia, but having tried that for about 20 years, it seems fairly unlikely to happen.

We believe that the models will be able to prospectively identify active agents. We believe that the models can be used for optimizing administration schedules and perhaps putting the appropriate schedule into the clinic at an earlier time.

We believe that the models may be useful for prioritizing agents that go into Phase I as there are many agents out there with little basis for anticipation that they will have activity in pediatric tumors, and we believe that the system may allow rational decisions to advance or stop development from the Phase I to the Phase II step, because Phase II trials in pediatrics, especially single institution Phase II trials can take several years and consume considerable resources.

I think the data from the animal models will certainly help us to focus Phase II trials where appropriate.

[Slide.]

So, in conclusion, valid models of childhood cancers do exist if they are used intelligently. Models reflect clinical drug sensitivity.

Species differences in drug disposition, metabolism, and tolerance are the major problems in accurately translating results.

The models accurately identify clinically active agents when systemic exposure is normalized between species.

[Slide.]

In terms of practical considerations, what do we need? We need access to drugs at an early stage. We need to establish a national consortium to encompass virtually all of the frequently occurring pediatric tumors.

We need to develop predictive pharmacokinetic models to translate data from the animals to the clinic.

We need to characterize available models through genomic or proteomic screens to identify molecular targets that are expressed in the pediatric tumors that may be the subject of drug development for adult malignancies.

We need to develop a funding mechanism to support experimentalists involved in preclinical to clinical translational studies.

In terms of characterization of current models using molecular techniques, this is an initiative developed through CTEP at the NCI through Malcolm Smith and Barry Anderson, and similarly, the idea of establishing a national consortium is also being led by the same two individuals and Peter Adamson, COG.

[Slide.]

So, this is the proposed schema for developing a national consortium with Tumor A through E, panels of different pediatric childhood cancers that will be evaluating drugs in various sites around the U.S. and perhaps abroad, but the idea is to bring in a drug, drug X from a pharmaceutical company, then, to screen according to the wiring diagram shown here.

The idea is to identify drugs that have a specific activity against a particular tumor at the MTD in mice, but then if so, to do a full dose-response curve pharmacokinetic work-up and, where appropriate, to use transgenic or orthotopic models as secondary screens after subcutaneous

xenograft evaluation, and then to take this data and, through central analysis, refer it back to the Developmental Therapeutics Committee of the Children's Oncology Group to allow and hope some prioritization of drugs going into pediatric trials.

What this clearly needs is a buy-in from the pharmaceutical industry where they will allow early access to drugs that are in early clinical trials to be put through the screening model with the hope of identifying drugs that will be helpful to pediatrics.

Thank you.

DR. SANTANA: Thanks, Peter. I am going to hold questions and comments because we do have a brief period after the three presentations, and these three presentations kind of carry the same theme.

I want to thank Peter again and then I am going to invite Ed to go ahead and give us his perspective.

Applying Preclinical Data to Clinical Studies

Edward Sausville, M.D.

DR. SAUSVILLE: Thank you very much. I am happy to have this opportunity to present a

perspective from the Developmental Therapeutics Program at NCI on these important issues.

I would like to, first of all, have a bit of a disclaimer. I am not a pediatrician, so the perspectives that I have been asked to address would be of general relevance as we apply them to adults, but as you will see, I think they raise a number of issues that will come up in the course of the day.

[Slide.]

The goals of preclinical drug studies proceed at least from a regulatory framework from the standpoint of deriving the data to support an Investigational New Drug application. This is approval by the FDA to conduct human studies, and the main criteria is safety and likely reversible toxicity to allow the start of Phase I trials.

There are a number of special issues that one could imagine coming up in the development of pediatric Phase I oncology drugs. There are relatively few things we compare to the adult population of patients, however, there are many agents, and therefore the question comes up of how we can best match the patients to drugs that are available that hopefully would ultimately benefit

them.

There is clearly an unmet medical need with respect to the patients in the pediatric population that come to the point of being candidates for this, however, there are ethical concerns in that whereas in adult, there is the capacity to make an informed consent and oftentimes in the populations that are selected for study, not the need for urgent response, this clearly is not the case in the pediatric population.

These patients in the pediatric age group frequently have seen much prior treatment, are on a number of concomitant medications, and therefore, how these might influence the experience of an initial first in human drug as applied to the pediatric population is a concern.

Lastly, as we have heard many times, pediatric patients have a unique biology both in the tumor and the host, and therefore the value of adult data in study design, I think is of issue and will be considered in this meeting.

[Slide.]

Now, the classical NCI recommendations that have governed the entry of new drugs--and this is from a paper from Sylvia Marsoni and colleagues,

she is now back in Milan, which emanates from her time at the NCI--is to begin studies in pediatric patients with solid tumors and leukemias at 80 percent of the maximal tolerated dose observed in adults with solid tumors. So, in essence, there would be prior adult data prior to beginning the pediatric studies.

To enter solid tumor and leukemia patients at each level, and escalate in fixed, 20 percent increments, distinguishing myelosuppressive toxicity that might be actually desirable in the leukemia population versus non-myeloid toxicity.

In the absence of non-myeloid toxicity, to escalate beyond the solid tumor MTD in leukemia patients, in children.

[Slide.]

However, there are a number of issues that have come to the fore that question this basis and urge every consideration of this classical practice.

First of all, from the standpoint of biology, pediatric tumors may have, and indeed have been demonstrated to have, targets that are intrinsically different from adults, and therefore adult data will never actually be available for

drugs directed to these targets.

From the standpoint of pharmacology, past practice is weighted toward cytotoxics. The question of the relevance of these practices to so-called "targeted" agents that might not have cytotoxic endpoints could be questioned.

Then, in terms of timing, there are many new agents. There has been an explosion of interest in the pharmaceutical industry and academia over the past 10 years, and therefore a delay in completing adult studies before application in pediatric neoplasms may therefore actually exacerbate the unmet medical need.

[Slide.]

Now, just to focus and clarify the components of an IND, and this is primarily for didactics, but in addition to the definition of the substance and the actual clinical plan, the critical issues in putting together the IND is the pharmacology and toxicology information and prior human experience that go into this.

[Slide.]

So, how are Phase I dose and schedule fixed in adults? Animals, usually mouse studies in models, define likely active schedules--and Peter

did a great job in illustrating some of the ways that these can be used--bearing human-derived tumors.

The likelihood of human activity is essentially stochastic, the more models with activity, the greater likelihood of human activity. Limitations, as Peter stated, are the difference between animal and human pharmacology and metabolism.

Drug concentrations or the effect on the target, as Peter illustrated, and particularly with respect to pharmacology, can provide very important ancillary information.

Toxicology is conducted according to a series of protocols developed by the NCI in the 1970s and which address the requirements of the FDA.

The starting dose is a fraction of a dose causing no or minimal reversible toxic effects, and escalation of dose steps occurs in a way that would likely capture a reversible toxic effect.

[Slide.]

So, what are the problems with so-called maximum tolerated dose driven endpoints?

Drugs regulating pathways important in

oncogenesis or tumor biology are effective by combining with high affinity binding sites, therefore, one must distinguish between targeted in comparison to non-targeted toxicity in relation to these binding sites.

Clearly, if the tumor or organism does not reliably express a basis for a targeted effect, there could be a misprediction of the potential value of the agent.

Whether dosing beyond the effect on the desired target buys additional therapeutic value is not clear. Therefore, an additional interest is to define, in preclinical studies, a biologically effective dose, as well as the maximum tolerated dose.

One could imagine, therefore, using a biologic rather than toxic endpoints in Phase I.

This issue is as important in the agents that are under development for adults as with children.

[Slide.]

Now regulatory considerations for preclinical development of anticancer drugs--again, this is an area that has been written about and discussed by many colleagues at the FDA--and in

this recent article from DeGeorge and colleagues, the types of preclinical studies expected for support of clinical trials has to consider the intended use of the drug, as well as the population of patients being studied.

In situations where potential benefits are greatest, greater risks of treatment toxicity can be accepted provided that they are addressing these at-risk populations and therefore the required clinical testing can be relatively minimal.

[Slide.]

The application of this through the years has led to a relatively abbreviated toxicology for oncology drugs where, in the case of small molecule agents, two species, one rodent and one non-rodent, and in usual practice, this is usually rats and dogs, are studied on a clinical route and schedule that again follows NCI guidelines. Although pharmacokinetics is optional in a regulatory sense, it is strongly encouraged.

Biologicals, in contrast, have a somewhat different approach where the focus is a most relevant species, and this is usually a non-human primate, again following the clinical route and schedule.

[Slide.]

The objectives in preclinical toxicology and safety studies are to determine in appropriate animal models, the maximum tolerated dose on the desired schedule and elicitation of dose-limiting toxicities, the definition of schedule-dependent toxicities, the documentation of the reversibility of adverse effects over the likely dose range to be studied with the goal of defining a safe starting dose.

[Slide.]

I list here the so-called standardized NCI protocols from a relatively earlier era where, in mice, dogs, and rodents, there is determination of lethal doses at various fractions of the dose range anticipated to be used in humans.

[Slide.]

Over the past decade, NCI toxicology philosophy has evolved somewhat, so that we now focus on so-called agent-directed studies that are importantly, pharmacologically guided and to integrate the safety studies with the preclinical efficacy data and the proposed clinical protocol.

This would lead to a rational evaluation of the role of schedule dependence,

pharmacokinetics, and metabolism in the development of toxicity, and relate plasma drug levels and area under the curve to the safety and occurrence of toxicity.

Actually, as Peter illustrated, this would be an important opportunity to correlate with activity in the preclinical models.

And, importantly, to extrapolate toxic effects across species.

[Slide.]

The goal of this is certainly a better scientific basis for development, greater flexibility in designing dose schedules, and allowing a data-rich IND submission to support Phase I and hopefully, in a variety of the ways listed here, optimize the Phase I experience.

[Slide.]

So, to illustrate this briefly, just so that everyone has a common viewpoint of how this proceeds, and all this data has been disclosed in various AACR and other presentations, Ishihara Sangyo Kaisha submitted a series of benzophenylureas, shown here, and using a series of pharmacology studies, it was possible to show that, in essence, the dimethyl was a prodrug for the

other forms and that this was chosen to move forward.

[Slide.]

In a variety of tumor xenograft models, there was percent tumor over control, no worthy evidence of activity on a schedule that was intermittently either parenterally or by an oral regimen.

[Slide.]

This led to toxicology studies that exactly mirrored that schedule. In the rat, the MTD was 360 mg/M2, in the dog, somewhere between 150 and 240, and therefore, this experience drove the determination of a starting dose, which as you can see was one-sixth to one-tenth of that maximum tolerated dose in the sensitive species. In both species, there was concordance of the toxic effects because at dose-limiting effects on marrow and GI tract were observed.

[Slide.]

In addition to this, in addition to the safety information, one determines what the efficacious drug levels in plasma are, correlates drug plasma levels and the area under the curve with toxicity and safety, and attempts to

ameliorate toxicity by changing the route and schedule, and compare toxicity with accepted clinical agents when that is appropriate.

[Slide.]

Just to emphasize the point that Peter made, and there are important influences on schedule and route and the appearance of toxicity, some recent examples are listed here. If one looks at penclomedine, when given as a bolus, neurotoxicity is dominating, when orally given, bone marrow toxicity dominates. So, this information is very important and routinely acquired before going into human experience, or we go back and do it after the human experience suggests it.

[Slide.]

So, how predictive of human experience are these safety-testing algorithms? In NCI data that will be presented in detail at the upcoming NCI-URTC-AACR meeting in Frankfurt, the predictive power actually varies somewhat with the endpoint desired.

If one wants to focus on a safe starting dose, if one uses 2 to 3 species including rodents and non-rodents, there is a 97 percent ability to

predict actually a safe starting dose. This drops somewhat if one uses the mouse only to about 83 percent.

But if one focuses on a correct elicitation of the human maximum tolerated dose, there, no one species is actually completely predictive. Rodents in particular are actually very bad at predicting the maximum tolerated dose. It gets a little bit better in the dog.

We are aware of no in vitro or in silico methodology that has yet emerged to predict human toxicity with the possible exception of efforts to use marrow cultures to distinguish between rodent and human sensitivities.

[Slide.]

This data actually mirrors the industry experience that was collated in a very useful publication whose reference is shown, where in data that was contributed by a number of companies, from a number of different therapeutic areas, if one looks at the concordance between occurrence of human toxicities that were observed in the clinic with what would have been predicted by the animals, 71 percent of the human toxicities were associated with some toxic experience in animals.

This was best mirrored by the non-rodents and very poorly or at least less well captured only in rodents, however, and this is an important issue, approximately 30 percent of human toxicities were not predicted by the animal experience.

Thus, if one considers a situation where there would be first in human experience in the pediatric population, one has to consider that one would be open, if one went forward with that, and using the current algorithms, to potentially experiencing new toxicities for the first time in the pediatric population, and that is something that this group I hope will consider.

The conclusion of this body was that two species are best predictors. Again, single species, if one is going to use, the non-rodent tends to be better than the rodent.

[Slide.]

So, consideration in applying these data to the pediatric population lead us to a number of questions, and I would just list these.

First, how closely do adult and pediatric maximum tolerated doses actually correspond? Is there a difference between cytotoxics and non-cytotoxics in this regard?

Are the determination of classical maximum tolerated doses still relevant if one is going to apply this primarily to the pediatric population, or should the age, maturity, or the nature of the tox species that is used be reconsidered if adult human Phase I data is not actually to derive pediatric dosing?

The importance of efficacy model pharmacokinetics and pharmacodynamics in guiding this, I think was well illustrated by Peter's talk and needs to be hopefully applied on a broader scale.

Another issue that deserves consideration is the chronicity, reversibility, and age-relatedness of target-related toxicities. For example, it is well known that anti-VEGF receptor antagonists have effect on the bone growth plate and therefore could be qualitatively different in their implications for use in the pediatric population.

The recently studied anti-EGF receptor antagonists likewise have a cutaneous toxicity that is relatively well tolerated by most adults. How it would extrapolate to growing skin and its implications is a matter that is certainly not

clear in the literature.

[Slide.]

I would like to acknowledge the contributions of my colleagues who are listed here to my presentation, who have importantly put together this data.

Thank you very much.

DR. SANTANA: Thanks, Ed.

We are going to continue moving forward and I will ask Pat Reynolds to get started with his presentation.

Applying Preclinical Data to Clinical Studies

Patrick C. Reynolds, M.D.

DR. REYNOLDS: Thank you, Vic, and thank you for the invitation, Steve.

What I want to address, you have heard about in vivo models, I want to address primarily in vitro models, but to also contrast a little bit about the kinds of things we might learn from in vitro models versus in vivo models in terms of preclinical drug testing in pediatric cancer.

[Slide.]

One of the models that led to successful clinical application of in vitro testing is shown here, which is studying retinoic acid. Initially,

this work was done with transretinoic acid and then it was recognized that we probably couldn't obtain the levels we needed in patients with transretinoic acid, so it was in vitro modeling, that is shown on the righthand panel, using a dose schedule that we thought would be obtainable in patients of essentially two weeks exposure targeting 5 micromolar levels, which got significant responses in vitro, and led us to do a Phase I study, which documented we could get those levels in patients, and then went on within the Children's Cancer Group to do a randomized study in which completing cytotoxic therapy patients were randomized to get either 13-cis-retinoic acid or no further therapy.

That showed a significant benefit for those patients randomized to get 13-cis-retinoic acid and has led to its incorporation within the treatment of high-risk neuroblastoma in most centers at this point.

[Slide.]

If one looks at in vitro testing of anti-neoplastic drugs, the assay systems that you use really need to have a wide dynamic range. Ideally, 3 to 4 logs of cell kill should be measured, yet, you need to still have a high throughput.

The cell line panel that you employ needs to have multiple cell lines. These need to include those that are not only the ones at diagnosis that are going to be sensitive to normal drugs, but the ones that are going to be resistant to the standard drugs used to treat the patients as we see them today.

Major mechanisms of resistance need to be identified and reflected in the cell line panel. Exposure to drugs should be done at clinically achievable levels and schedules.

As hypoxia is known to antagonize a number of drugs in terms of their antitumor action, testing really needs to also be done under hypoxic conditions.

[Slide.]

Now, the limitations of in vitro testing are well known. One is the selection for cell cultures for their ability to grow in vitro, might not reflect the human condition.

Artificially high drug exposure can occur in vitro, and one has to be careful to look into that when one is designing these types of studies.

Cell culture oxygen conditions in standard incubators far exceed the physiological, and one

needs to take that into consideration.

Cell-to-cell contact, especially with normal cells, is not preserved.

But if one designs the types of preclinical testing that one carries out to take into consideration these sorts of limitations, it may be possible, as we have seen at least with the one example I showed you, to use in vitro data to move forward a drug successfully into the clinic.

[Slide.]

Our approach is to use a very high throughput, high dynamic range system in which we have digital image microscopy that works with an inverted microscope to measure in 96 well plates, viable cell numbers, and shown on the righthand panel, you can see the dynamic range goes through 4 logs if one seeds the viable cells into a plate in the presence of excess dead cells.

This relies upon fluorescein diacetate, which shows you the viable cells, and you can see here in one of these images from a microwell that you can easily recognize the viable cells as being brightly stained, and this is what the computer is essentially recognizing.

Using this system, we have characterized a

number of neuroblastoma cell lines, and this shows you the panel we selected, which encompasses those at diagnosis, shown on the lefthand side. In the middle are patient samples that were placed in the culture after progressive disease, during induction chemotherapy, many of which are matched to those from the diagnostic specimens.

Then, those placed in the culture at time of recurrence after myeloablative therapy. As you see, the fold resistance to the drugs tested in this particular experiment, which was a carboplatinum, cisplatinum, melphalan, doxorubicin, etoposide, all commonly used against neuroblastoma, clearly goes up to some degree when one gets recurrence after induction chemotherapy, but clearly, there is a high degree of resistance occurring after transplant as one might expect, and this is sustained resistance.

It is, in fact, those cell lines that we feel allow us to select new agents better because these are, in fact, the kinds of tumors that we are going to see if you are going into Phase I or II setting in the children since most children are now treated with myeloablative therapy before they recur.

[Slide.]

One of the types of agents we have worked up in vitro with that system is a glutathione depleter that we obtained from the NCI, buthionine sulfoximine or BSO, and this shows you the dose-response curve in red for melphalan, by itself in this cell line, adding melphalan plus 1 micromolar BSO.

Keep in mind the adult experience was that continuous state levels of 500 micromolar BSO were obtainable. That caused a significant sensitization. You go up to just 10 micromolar BSO, you get a really tremendous sensitization in this cell line.

[Slide.]

In fact, this is work by Clark Anderson at Children's Hospital, L.A., and within the NAT consortium he had done a pilot study. This shows you one of the patients from his 30 percent response rate he saw in the pilot study in which recurrent neuroblastoma after multi-agent chemotherapy, saw a dramatic shrinkage of tumor treated with BSO melphalan.

In this particular study, there were no stem cells support given, so we were limited in

giving the melphalan to doses that were tolerable with the amount of product toxicity that was going to occur, and there is currently a Phase I study ongoing looking at dose escalating the melphalan in the presence of BSO, which we expect would achieve even a higher response rate.

Again, this is another example of an agent moved into the clinic that has shown responses in the clinic all based upon in vitro testing, and not xenograft testing.

[Slide.]

Now, xenograft models for drug testing, which you have heard elegant work from Peter already, from the St. Jude's group, and of course others doing similar types of work, these provide another way of looking at drugs and one that certainly gives you kinds of information that you can't get in vitro.

The kinds of models that you use there, I think you need to use, as Peter has shown, signs that are responsive and resistant to standard agents. Subcutaneous xenografts allow for easy measurement, but most pediatric tumors don't present as subcutaneous tumors, so one has to consider other types of models.

There is a lot of work going on in a variety of laboratories looking at intravenous injection to mimic minimal residual disease in nude and SCID mouse models, and immunocytochemistry can detect that MRD and characterize it.

The new rodent imaging models are methods that can be applied to these models, allow for assessment of response in organs, potentially in a variety of organs. To just show a sort of example from that, I am going to show you in a moment the kinds of things one can do with that.

[Slide.]

The limitations of rodent models for drug testing are as follows. One, as you have heard already, the pharmacokinetics in the mouse is certainly different from the humans, as applicable to testing the efficacy as it is the toxicity, as pointed out already by Edward.

The adult mice, as well as adult dogs, I might add, are what is used for this testing. One cannot use the pediatric model in this setting, so that might be a limitation.

Animal testing is clearly labor-intensive and expensive. The subcutaneous tumors may be quite different than the orthotopic setting, and

transgenic animal models, while interesting, I think we need to keep in mind that if those are used for drug testing, they will be providing virgin tumors that have not yet developed resistance to currently employed drugs, and this has to be considered in applying data from those types of models to going into the Phase I and II setting.

[Slide.]

Just to show you an example of the types of imaging that is coming out now, and there is even more exciting stuff coming with the luciferase assays and the micro-PET scanners, but one can get high resolution radiographs now and pick up bone metastases in these mouse models, which can be confirmed, as you see in the center panel, by histology.

There are even micro-CT scanners available, which although a little more labor-intensive than the plain films for doing this routinely, certainly confirm the results that you get with plain films or histology.

[Slide.]

So, for drug testing in pediatrics, what results should encourage pediatric clinical trials?

I would suggest that multi-log killing of cell lines, multiple cell lines, including those established at relapse, and this obtained at clinically achievable drug levels, would certainly be one criteria that should encourage us.

Activity against multi-drug resistant cell lines in hypoxia should be considered because the tumors that we see in these patients will not be presenting in 20 percent oxygen, so that has to be a component at least of in vitro testing. It is already a component of the in vivo testing that we see in xenografts.

Responses in xenografts, ideally in those that are multi-drug resistant, and significant activity of drug combinations might encourage Phase I trials even if the single agents show only modest activity.

So, I think that using the laboratory to work out combinations is something that has been under-explored and should be emphasized in this sort of work.

[Slide.]

What results should discourage pediatric clinical trials? I think poor activity, i.e., less than or equal to 1 log of cell killing at

clinically achievable drug levels in multiple cell lines might want to make us think twice about whether or not to move forward.

Obviously, poor activity in xenograft models known to be responsive to standard drugs would be another, although we need to be careful because if one is doing a xenograft model, and one can obtain much higher levels in the human than one can in the mouse, then that would not be used to discourage you if you know you can get in the human with the higher levels.

Availability of agents with more promising activity for the same target population should factor into this, so one should take the sum total of the data together and apply it if one does not have a lot of agents in the pipeline that look interesting, one still may want to move forward an agent, whereas, if there are a lot of agents, one may want to think twice.

In other words, the whole concept that we have all been discussing in the NCI consensus panels that Malcolm has put together has been one of prioritization, there is no black and white.

[Slide.]

In summary, preclinical drug testing may

be a means of prioritizing new agents. There are a variety of models for doing that, and these need to be studied.

Validation of the existing models should be undertaken both retrospectively, as well as prospectively, against the basis of clinical data we already have from the cooperative groups and individual institution trials on agent activity.

Preclinical modeling of drug combinations may facilitate the design of Phase I and II studies, and those should be explored, as well.

Thank you for your attention.

Committee Discussion

DR. SANTANA: Thanks, Pat.

I think we are going to take a few minutes to have comments and discussion on the three presentations that we have visited regarding preclinical models.

I want to start by asking Peter a question, and that is, do we have any sense based on all the data of xenograft models what the false negative rate is? That is, that there is a drug that we have tested in xenografts that we have said for X, Y reason, it is not active, we are not going to use it, but then ultimately, there has been

experience clinically with that drug, and actually it has been found to be active.

Do we have a sense of what that threshold of false negativity may be?

DR. HOUGHTON: I don't think we do with respect to the pediatric models although we can look at the drug, such as etoposide, which is clearly very active, and that may be one example where the mouse model under-predicts activity, because in the mouse, etoposide is cleared very rapidly relative to that in children.

So, that would probably be the best example of a false negative in the model systems, but I think if you use the models and you relate tumor response to pharmacokinetics, then, even if we had that data showing relative lack of activity, and some tumors do respond, but it's not dramatic, and we had the adult data showing the PK was maybe five, 10 times higher, I think that would be a reason not to preclude that drug from pediatric trials.

The whole ongoing process of model development is an experiment. I don't think I intended to indicate that if a drug didn't show activity in the sort of broad panel of models that

we presented as a potential consortium, that that would preclude a drug going into the clinic.

In fact, it would be very useful if those drugs did go into the clinic, because we need to do experiments that validate that preclinical models do have any role.

DR. SANTANA: I have got one follow-up with a comment that you made, which is this issue of using preclinical models in the new era of biologics, because I think we are so used to these preclinical models helping as standard cytotoxics, but I want to hear more thoughts from you or from your group and how we can apply the models that we currently have to try to address these issues of the biologics, which may be completely different, and we are going to have to face in pediatric, too, because they are going to be used.

DR. SAUSVILLE: I think you touch on what is also an emerging experience, and I wouldn't want to imply that there is substantial data to support one position or the other.

What does seem to be emerging, and this is very much on the plate for oncology, drug development in adults, is that there is a disconnect between the science that develops the

drug and then the clinical testing that goes on.

In many cases, companies will launch fairly large Phase II and even Phase III trials with essentially no data as to the expression of the target in the population, whether the pharmacology that they are observing in the adults actually addresses the targets.

So, I think there is a lot of concern, and we can point to recent, shall we say, less than optimal outcomes in terms of such experiences. An example would be the matrix metalloprotease situation where one has to consider whether not characterizing the effect of the drugs on the target as part of the clinical development scenario has really compromised the ability to make progress in these areas.

What that means to me and to many of us at NCI is that we are strongly encouraging the grantees that we work with to develop protocols where the assessment of the molecular target addressed by the drug is built in, if possible, to some aspect of the drug's development process.

We are very interested in supporting preclinical modeling efforts where in addition to the pharmacology information that relates to

efficacy and toxic effects, pharmacology information related to the effect on the target could be very important to have available in decisionmaking.

So, we can only stand in the bully pulpit, so to speak. I think this is going to require a bit of a behavior change on the part of people who do clinical trials, and also it is going to require an advance in diagnostic efforts, so that you can easily diagnose the presence of the target in these different populations.

DR. SANTANA: I think a follow-up comment to that, I don't want to monopolize the discussion, but a follow-up to that is the whole issue, I was impressed by your one-third of the times that your model cannot predict the toxicities that will occur in humans.

I have a suspicion, and I may be completely wrong, I have no evidence to have the suspicion except to say it may be much higher in biologics if the preclinical models cannot adequately assess the toxicity in those scenarios.

Who was first? Go ahead.

DR. GOOTENBERG: I am just speaking from the viewpoint of FDA biologics. We certainly take

that into account in the ways that we would like to see the starting doses as a certain safety threshold below the NOAEL level, not below an MTD in preclinical models, and we also are very interested in assessing optimal biological doses, the same as you are saying, in many of these models where an MTD is really not a rational goal.

DR. PRZEPIORKA: Two quick questions for Dr. Sausville.

First, you indicated that the animal models do not accurately predict the human MTD, and cited NCI data as your reference. Was that based on mg/kg or actual drug exposure, and do you know if there is a difference between the predictability if you do this based on drug exposure rather than mg/kg?

DR. SAUSVILLE: It was ultimately done on mg/kg or basically bioservice area issues. It has not been normalized with respect to pharmacology issues. You are quite correct that there might be a better refinement if one considers that.

DR. PRZEPIORKA: You also raised the question about whether or not the adult and pediatric MTDs correspond. At a previous meeting, we had talked about they may not correspond and

that there is data out there that can be looked at to see whether or not we should change the 80 percent rule.

Since that time, I was wondering had anybody gone back and looked at that data to see whether or not that rule is truly valid.

DR. SAUSVILLE: On that, I would have to defer to my colleagues in the pediatric part of CTEP. I think one point that addresses--again, I am speaking from data that is in the literature--one does have the impression that with the passage of time, the ratio between the MTDs is changing, so that there is a better correspondence currently than there was in the past perhaps.

Again, I think that is a cytotoxic-driven sort of experience, so while I believe that at one level, such an analysis that you described may be fruitful in refining the basis for that, I also think, as was pointed out a few minutes ago, really addressing concentration that addresses the target modulation is going to be real important, at least as equally important to me in making that consideration. Malcolm or Barry, you may want to comment.

DR. ADAMSON: I think that everyone should

start with an edge is on target that, because of the changing nature of the patient population that are studied, both adults as well as pediatrics, the differences, the divergent differences that we have seen (inside topics) are, I think, fewer at this point.

For the biologics, we have had some experience of, in fact, there may be significant differences in tolerability and the 80 percent rule is probably not a relevant rule for some of the biologics because children, at least in certain situations, may be more sensitive to the biologic toxicities of some of these agents.

So, we don't have a lot of preclinical data that can guide us on this front, and I think on an agent-by-agent basis we have to have discussions and considerations as far as where we ought to start.

We are usually, however, not a log away from where we end up. We are not sort of held to the same limitations. Because we have the adult experience in front of us, we don't necessarily have to start at one-tenth of a mouse dose and have multiple escalations.

What, in general, we are talking about is

the addition of one or perhaps two additional dose levels if we have concerns about the tolerability in children.

DR. BLANEY: I would just like to make a comment that sometimes the MTD that we define in the Phase I setting isn't ultimately the dose that patients in the front-line setting will tolerate. They will frequently tolerate more, at least with the cytotoxics, so the Phase I is only the first step and further dose refinement may need to occur earlier in front-line treatment protocols.

DR. HIRSCHFELD: I had a question, which is a more general one, so any one of the panelists or anyone else with a thought in the area could respond.

There was a distinction made between biologicals and cytotoxic drugs. What I would want to ask is, given our current knowledge of the various preclinical models, are there sensitivities which are driven by the type of agent, that is, is it the therapy which is determining the sensitivity and specificity of the model, or is it the tumor types that are in the model which are then more critical.

I know the answer can be, well, a little

of both, but I just wanted to raise the issue that maybe for some classes of drugs, if that is the case, then, certain models might be appropriate, or if it turns out that it is the tumor and it doesn't matter what you throw at it, that it is always going to be predictive, then, that would be another scenario.

DR. HOUGHTON: I think if the latter is correct, then, we are in trouble, because we are developing molecularly targeted drugs for specific reasons, and if it doesn't matter if your target is there and the tumor responds, then, we are doing something wrong.

I think what we would like to achieve, and, Malcolm, correct me if I am off base, is that with the pediatric models that are available, is to characterize them, so that we can identify potential targets that may also be the targets for drug development in the adult population.

So, then if there is a specific kinase inhibitor that is being targeted for adult treatment, because that particular kinase is over-expressed in tumor X, then, we could at least focus the use of that drug against the models that express the target or over-express the target as a

first attempt to see whether target inhibition relates to tumor response, and we can do this quite readily in the animals, much more readily than we can in the clinic.

The second step would be to say does the drug have a wider application than just the tumors that have the over-expression of that target, and I think with that sort of data, we may well be able to answer the questions you raise, but I think at the moment, the data is not available to definitively answer the question.

DR. SAUSVILLE: I would point out that of the data that exists, it is sending a mixed message. I mean if you look at the experience with STI571 and bcr/abl, there, there was an exact correspondence between the behavior of the regular old xenografts and the target in the regular old xenografts, and we all know the story.

If you look at the history of the farnesyl transferase inhibitors, there, it has been very divergent, where the animals at one level or another greatly increased enthusiasm for agents that, at least in their initial iterations in the clinic, have been somewhat more problematic.

DR. SANTANA: Any other further comments

or response to Steve?

DR. SMITH: I would just echo what both Peters said in two comments. One is we do have an ongoing project where we are attempting to collect a panel of pediatric cell lines and xenografts, so that those can be characterized molecularly, so that that can then inform both in terms of their gene expression profiles, but also tissue arrays and protein arrays, that can inform the issues of molecular targets for specific childhood cancers, and inform the preclinical testing process.

The second point, to echo Peter Adamson's point or Susan's, that when we started, between 60 and 80 percent of the adult MTD, we are not logs off.

You know, typically, we are either at the MTD, we are one or two dose levels below the MTD, or you have to drop back one dose level, so essentially, you know, it remains a very efficient way to introduce a drug with relative safety into the pediatric population, and then, you know, to determine a dose in this heavily pretreated population, recognizing that when we go forward, we may have to make additional modifications in less heavily pretreated patients.

DR. WEITMAN: A comment and a question.

We certainly did look at recently some of the changes in MTDs between adults and children, and there has been a trend with the cytotoxics at least for a decreasing margin or difference between the two.

I think when we looked at it in more detail, it was due to the fact that certainly the kids that were going into Phase I studies were much more heavily pretreated, mostly transplant allogeneic, autologous transplants, radiation compared to a lot of the adults that were going on study are very minimally treated, in fact, sometimes no prior treatment at all, so I think that was affecting at least for cytotoxics. That is a comment.

I guess as a question for either Pat or Peter, looking at the schematic, particularly that Peter showed, can you give us some idea I guess of the time frame to develop a gestalt for an agent, whether you think it is going to be active or not and warrant going into pediatric studies, particularly going through either that schematic or cell line studies, again, a time frame.

DR. HOUGHTON: Ultimately, we would like

to start by screening 15 drugs a year through this, and that is a study of in a sort of conservative way, so I would imagine a first cut to show any activity would be on the order of three months, and then if we showed activity, say, in neuroblastoma models, to run through the dose-response curves, would be another three to four months.

So, we are talking about a six- to nine-month period of generating data, which is not a terrificly long period, I think.

DR. WEITMAN: Would that be different for cytotoxic versus targeted therapy where you could potentially feel that there may be more molecular studies that would need to be done to validate the model?

DR. HOUGHTON: I think we have to be very specific as to what the screening program is, because you could expand it to the point that it becomes so huge and all encompassing that you would never get anything done.

I think the initial experiments will have to be to evaluate a drug in terms of its antitumor activity. A secondary component of that would be target validation in terms of target inhibition, but I think that has to be done outside this

initial screen.

It may be that particular labs would look at that outside the screen. I think the initial screen is set up to look for antitumor activity as the primary function. It may develop beyond that, but I think we have to be focused in the design of the experiment at the front end.

DR. SANTANA: Pat, do you want to add onto that as it relates to the cell lines?

DR. REYNOLDS: I think that the time frame that Peter is discussing can be compressed a little bit for cell lines, but then if one sees activity, one would probably expect to be going into xenografts, as well, so I think the time frame would be very consistent, and probably both could go on simultaneously and kind of cross-feed upon each other as far as making decisions.

DR. SANTANA: Steve, I will give you one last prerogative.

DR. HIRSCHFELD: I will try to be brief. Although my job description is to remain in equipoise, I wanted to point out that historically, the first targeted therapy was 6-mercaptopurine in 1952, and it is, as far as we know, quite targeted, and some of the agents that we are calling

cytotoxics, such as the topoisomerase-1 inhibitors that were discussed this morning, are also quite targeted.

I don't want us to be misled by putting a distinction which may be more semantic than biologic.

DR. SAUSVILLE: So then my point is that that exactly illustrates the issue because you don't select patients based on any peculiarity of purine metabolism. You basically take all comers. So, I submit that that illustrates the issue.

DR. HIRSCHFELD: Well, we could pursue that, but many of the therapies that have been considered targeted, in fact, you used STI571, in fact, have been shown to be relatively promiscuous in terms of their partners within the cell.

DR. SAUSVILLE: Only if we were perfect.

DR. SANTANA: Let's move on to the second set of sessions. If anybody needs to take a break, please feel free to do that on your own, but I think we need to move forward.

I am going to invite Peter Adamson to give the Children's Oncology Group perspective on the current practice.

Current Practice

Children's Oncology Group Perspective

Peter Adamson, M.D.

DR. ADAMSON: Thank you, Victor, and thank you, Steve, for the invitation.

First, I want to apologize, you don't have the slides in front of you. I finalized them on the plane home from the Middle East yesterday, and I use the term "finalized" loosely. Then, we transferred them over this morning from the MacIntosh to Windows, and knowing Microsoft's history as far as making software incompatible with itself, I have no idea what these are going to look like.

[Slide.]

Having said that, I wanted to step back before answering some of the questions that Steven has posed to convey a sense of urgency that we, in the Developmental Therapeutics Program at the Children's Oncology Group, feel about the importance of moving drugs into Phase I at an earlier stage and in a more efficient and scientifically rational manner.

The downstream effects of every year that goes by while we discuss can we move them earlier have been profound, and our ability to really

substantially change therapy for children with the introduction of new agents has been hampered by a number of factors, so this is a critically important issue for us.

The reason it is important, I think we have to step back for a moment and look at what has happened in the treatment of childhood cancer from the 1960s to the current generation, 1990s, and overall, it is a remarkable success story when you look at it, and it is driven in part by acute lymphoblastic leukemia, such that today, approximately 75 to 80 percent of newly diagnosed children will be cured by current therapy.

There are some clearly highly successful tumors including Wilms' and select populations. Acute myeloid leukemias lag behind, but I think you have to look deeper than the overall success of the program to understand why we think this is such an urgent issue.

[Slide.]

Now, looking at the Children's Cancer Group studies of the high-risk neuroblastoma patients from two generations, the first 1978 to 1995, you can see that in that generation of studies, there were very few long-term survivors.

Now, primarily through dose intensifications, as well as the introduction of a biologic agent, there has been an improvement, but nonetheless, and even I think the most recent study, there will be a step up, despite the great intensification of therapy, we have a long way to go, and neuroblastoma is just one example, but there are a number of pediatric malignancies that have been a great challenge for us including gliomas, brain stem gliomas, metastatic sarcomas, and the list will go on.

Importantly, it is not that we have a select population of tumors where our cure rates are unacceptable, but it is the price that children are paying to achieve even the good cure rates.

[Slide.]

As shown here, are data from an intergroup rhabdomyosarcoma study of a 1,062 children and the number of patients that at any point during their therapy, experienced anywhere from mild to life-threatening fatal toxicity.

As you can see, approximately 80 percent of children at some point during their therapy experience life-threatening or fatal toxicity. This is really the face of pediatric oncology today

for many of our tumors.

Moreover with pediatric patients, not only do we have the concerns about life-threatening and fatal acute toxicities, we have the issues of chronic toxicity.

We all know the stories of anthracycline and the lifetime cumulative dose dependency, but what has clearly emerged over the last five to 10 years is that the risk of cardiotoxicity doesn't go away, that these children, as they enter into their early adulthood years, are experiencing increased risk of cardiotoxicity.

So, it is an urgent issue for us to try to move new agents forward in pediatric drug development.

Now having said that, let me give you an idea of the paradigm I think we can move towards, and it has been mentioned here already, and that is the story of Gleevec. I illustrate it to show, in part, the ability of the Children's Oncology Group to capitalize on advances made in the laboratory and in adult studies.

[Slide.]

Now, we completed a pediatric Phase I trial of Gleevec in approximately a 12 month time.

We determined the recommended dose, did pharmacokinetic studies, and we learned in this study that the pharmacokinetics in the children who were entered, and I believe all but one child had evaluable results, pharmacokinetics for this drug were, in fact, quite similar to the pharmacokinetics observed in adults, and finally, we examined responses.

[Slide.]

This trial was limited to children with Philadelphia chromosome-positive leukemias, and indeed, similar to adults, we observed responses both in Philadelphia chromosome-positive CML, as well as a small number of patients with ALL and AML.

We had a recommended dose, and we are now moving it forward. For this drug, we recognized that there are a number of potential targets in addition to bcr/abl, and these include PDGF-R, as well as c-kit.

What we can ask ourselves is, well, what is our base of knowledge for pediatric tumors for these targets, and it is somewhat limited, but not completely limited, and if one just looks at various types of data from functional data, as well

as expression data, there are a number of tumors that this drug might be important to look at.

We would certainly like to have additional preclinical data if impossible to narrow the field, but certain tumors obviously, we have the adult data to go on, but osteosarcomas, synovial cell, Ewing's, and desmoplastics, there is at least some evidence to suggest that these targets may, in fact, be relevant.

We clearly need better preclinical data, but we are not looking right now at a broad-based testing of this.

[Slide.]

To get more to the questions at hand, what are the criteria we use for moving an agent forward in pediatric Phase I? I put the terms in quotes, because I can tell you historically where we have been, where we are now, but I think the future and what we have worked with Peter and CTEP on, is going to rapidly change the criteria that apply.

The first one is availability of new agents for pediatric studies. I don't think I can emphasize enough that this has been the primary criteria that we have utilized. Any agent that we have had access to, in good part, we have moved

forward, and the reason is we haven't had access to enough agents, so any agent that we could move forward into pediatric Phase I studies, we have.

This is not an acceptable criteria. There are too many agents out there. We cannot be limited by the availability of new agents. We have to bring science into this. But I would be lying to this group if I said we have applied scientific principles over the last two decades when we have moved new agents forward.

We have learned about these new agents, we have studied these new agents, but the criteria, the overriding criteria is has the agent been available for study in the pediatric population.

We do look at the relevance of drug target in pediatric malignancies. Gleevec is certainly one example, but we are increasingly trying to apply this.

Activity in preclinical model systems has been increasingly important, and Peter Houghton has demonstrated the potential impact of using preclinical models combining pharmacokinetic data in the models to pharmacokinetic data in humans.

In pediatrics, we do have the advantage of when we decide to move an agent forward, that we,

in fact, have some exposure and tolerability data in adults. The examples that he cited with MGI will indeed influence our decision to move an agent forward in drug development, but we are not just looking at a model system purely to screen a large panel of agents, we are looking at the model system in the context of human drug exposure and human malignancies.

Finally, we do look at the experience in adult clinical trials, and certainly activity that is observed in adults will influence our ability to move that drug forward.

[Slide.]

So, if we can look graphically at the timeline of pediatric drug development in reference, in comparison to that with adult trials, there have been a number of agents that we have moved into pediatric Phase I following drug approval, when they have been on the market and in Phase IV.

I would say the largest fraction have been when the adults are in Phase III. Phase II trials have been completed, pivotal Phase III trials are going on. We begin our Phase I studies in children.

A smaller number, we have successfully moved into Phase I when the adults have been in Phase II, and I would have to think long and hard for the few examples when we have moved into Phase I when the adults were in Phase I.

This situation, I think we will have to change, and I think we can safely change it. We can use data from adult studies, pharmacokinetic, pharmacodynamic, and in the future perhaps pharmacogenetic, to start Phase I testing in children certainly when it has completed Phase I in adults and entered Phase II, but, in fact, potentially, when it is still in Phase I in adults.

[Slide.]

What are the limitations of our current approach? Historically, patient numbers were the rate-limiting step for pediatric Phase I trials, not that the number of children with cancer has changed over the past decades, however, the current situation is that there are an insufficient number of new agents available for study in pediatric Phase I trials.

There are a number of reasons for that, and they are certainly not all regulatory reasons. The impact of this, however, is that Phase I trials

initiated following drug approval for adults results in use in children without any pharmacologic, safety, or efficacy data.

When these drugs are available for adults, they are being utilized in children. We can spend a great deal of time discussing when we should get data, but once they are on the market, they are going to be utilized, and unfortunately, if we haven't even begun a Phase I trial, let alone complete it, we really have no basis for making a recommendation on how to safely use the agent in children, let alone to decide whether the agent has potential for efficacy.

[Slide.]

Now, the Children's Oncology Group during the merger of the four pediatric groups and the two pediatric cooperative experimental therapeutics groups has reorganized and currently, there are 21 centers in the United States.

Now, these centers weren't chosen for geographic reasons, but rather these are the most highly productive and committed centers to childhood drug development. The reason I point that out is to highlight the current commitment and efficiency in recent studies that have moved

forward in Phase I in the Children's Oncology Group.

[Slide.]

Now, right now we are trial-limited, and again there are a number of reasons for that, but we have three agents under study in Phase I that have broad-based eligibility criteria as far as histologic diagnoses. We have one that is limited to neuroblastoma.

We have a number of Phase I trials that truly are in select populations either for select CNS tumors or for hematologic malignancies also.

Now, for the broad-based solid tumor studies, one of the big issues is that these studies of dose levels are literally filling in less than 15 minutes. When we have a study, as you know, we enroll three to six patients at a time, but they are truly cohorts of three, we open it up in Children's Oncology Group, the dose level is filled within minutes, and we have web-based systems to do that.

In fact, because of the rapidity of this, we have had to develop waiting lists for these trials. Clearly, this is not acceptable. We need a significant number of more agents in Phase I if

we are going to capitalize on the efficiency of our current systems.

There are going to be another cohort of Phase I trials opening that will still leave us with insufficient numbers, and although we can't at this juncture say what is the optimal number of trials for available patients, it is likely to fall in the 8 to 12 Phase I trials that are open concurrently to fill the pipeline at an efficient rate.

Needless to say, these would only be agents which we believe have potential relevancy for pediatric malignancies, and given the current explosion in new agents, I think we would be able to, with additional resources, looking preclinically, help prioritize among them.

[Slide.]

So, I will emphasize what Peter said earlier. We need to improve early access to new agents for preclinical studies. The consortium that is being set up under the leadership of Malcolm and Barry at CTEP, and with a great deal of industry input from a number of people in this room, we, at the Children's Oncology Group, I think can help us prioritize amongst the new agents, but

access remains the critical issue.

I believe we can safely initiate Phase I trials of select agents. This is not to imply we should study everything in the pipeline at this stage, but select agents, I think we can safely initiate once the initial cohorts of adult patients are evaluable in Phase I, when we have pharmacokinetics data, or when there is clear evidence of biologic activity.

We cannot continue to wait for Phase III results in adults. We do have to strike a balance between the evidence in preclinical models, as well as data from adult, and trying to move the timeline forward.

So, those, I believe were all the comments I had. I think you are going to probably wait for questions.

DR. SANTANA: Yes, we are going to wait. Thanks, Peter.

I am going to invite Steve Weitman.

Industry Perspective

Steven Weitman, M.D.

DR. WEITMAN: I would also like to thank Victor and Steve Hirschfeld for the invitation today. I also apologize, as Peter did, for not

having slides available. I wasn't quite as at a glamorous place as Peter was in the last three days, at a CLGB site visit, so I did my slides on the U.S. Air flight from Durham last night up to Washington. Again, I apologize if they are a little out of order.

[Slide.]

What I wanted to do is give a little bit of the industry perspective and company perspective. I do feel fortunate that I have a fairly extensive background in pediatric drug development, but now also at the industry side, to have a pretty good idea of sort of both perspectives and understanding the problems that both sides face in developing and answering the questions when drugs should be developed in children and what resources we like to have at hand before we make that decision to move forward.

[Slide.]

In an attempt to really get to this, I posed three different questions, and that is, again, in the development of a new oncolytic, when should pediatric studies be undertaken, what factors influence that decision, and lastly, maybe a little bit out of the line of this discussion,

though I thought it was of interest to this group, should pediatric studies be performed only by cooperative groups.

[Slide.]

To really address the first question, again, when in the development of a new agent should pediatric studies be undertaken, I thought historically, just to get some background, I went back and looked at some of the drugs that have been approved within the last 10 years just to get some idea of when was the first adult study actually reported as compared to when was the first pediatric study actually reported.

These are approximate times because as you go through the literature, you always find a little bit of data here and there in children, but really true studies, and as you can see here, over the last 10 years, the average time between an adult study being reported and a pediatric study being reported, was around five to seven years.

Certainly, I think everyone would agree, based on what Peter just said, and from what we can see in the literature, that this is truly unacceptable.

I get the sense looking at some of the

more recent studies and interest, though, that this difference may actually be narrowing and becoming smaller, and again, whether this is due to the Pediatric Rule, FDAMA, the Best Pharmaceutical Act for Children, I think it is too early to really tell, but my sense is, looking at some of this early data, that this difference may actually be becoming smaller, which obviously is the focus of this meeting.

[Slide.]

One of the efforts that we did do, and I will put this as sort of interim results, I also posed these questions that I had in the slide to the ASPH/O group, which is again the American Society of Pediatric Hematology/Oncology, just when should pediatric studies be undertaken.

So far we are up to now about 125 responders, and clearly I think the ASPH/O responders felt that these studies should actually be undertaken during the adult Phase I studies, maybe not a surprise to most of us here. Some felt, actually, about a third felt that they should actually be undertaken after the adult Phase I studies, and a few rare individuals felt they actually should be undertaken before adult Phase I

studies.

[Slide.]

Question 2. What factors influence a decision whether or not pediatric studies are undertaken?

[Slide.]

Again, not necessarily copying Peter's slide, but historically, these are the factors that I came up with, which remarkably I think mirror exactly what Peter has shown - preclinical data, pediatric preclinical data. Drugs with new mechanisms or targets. Positive data from adult Phase I or Phase II studies, and then availability of drug for pediatric studies.

Again, we asked the ASPH/O responders to rank these on a scale of 1 to 7 with 1 being the least influential and 7 being the most influential.

[Slide.]

To date, this is what we have seen so far, that clearly, the more common response, the strongest response was for the presence of some preclinical pediatric data as a major driving factor that would influence whether a compound goes forward into Phase I studies.

As you can see here, there are a number of

other areas, and surprisingly, just as Peter has alluded to, availability of drug continues to be one of the major factors to influence a decision whether a compound goes forward, not whether it is active in adult studies, not new mechanism, just can you actually get ahold of the drug.

[Slide.]

Lastly, Question 3: Should pharmaceutical companies conduct pediatric studies outside the cooperative groups?

I think there was a pretty clear evidence that there is an opportunity there or an interest at least from ASPH/O members to conduct studies outside of the cooperative groups. Clearly, about half of the individual responders felt that this is the case.

[Slide.]

If you look at the reasons why we shouldn't do this, clearly, the most common answer was that this is just too small of a population, we are already at competition for patients for Phase I studies, and we really shouldn't have studies being conducted outside of the cooperative groups.

There were a number of other comments that were shared including clearly no, it would be a

terrible mistake to do, conflicts of interest, cooperative groups have been the cornerstone of success in pediatric studies, and all agents and studies should stay within that group, you know, the more convincing studies are done within the cooperative group setting, and then the cooperative group mechanism in concert with industry and NCI should be able to be the approach to take to meet all requirements both of industry and then FDA.

[Slide.]

When you look at the comments as far as why they should be conducted or that conducting studies outside the cooperative group is acceptable, clearly, I think the interest was speed, that the cooperative groups are congested, and that trying to do this outside of them, there may be an opportunity to help speed along the development of some of these compounds in this particular arena.

Again, this was from the ASPH/O survey that we did that is still ongoing and may be updated as more information becomes available.

[Slide.]

Now, to get at maybe the question that Steve actually posed to me, and again, what is sort

of the company perspective on this, I would say that each agent really needs to be considered separately and independently, that there isn't really any standard approach to say yes, all agents go into children as quickly as we can.

I think there is a balancing, that we have to weigh a number of factors. What I would say, early pediatric studies, I would agree with Peter that I think getting them in during adult Phase I or Phase II studies is on the early side. Later pediatric studies would come when the adult Phase III or Phase IV studies have been either completed or at least ongoing.

Now, what factors influence I think at an industry level whether a compound would go into an early pediatrics arena, and I would put down certainly medical, scientific perspectives if there is a similar disease process, such as leukemia.

We have a drug that we are interested in, in looking at its use in leukemia. We feel that there is a similar disease process there, so that is a drug that I think warrants going into early pediatric studies.

Also, if there is a similar target expression, such as Gleevec, I think that again

sways us towards wanting to put this drug into early pediatric studies.

I think there are a couple other factors that again are a little bit outside of what has been mentioned already, but I think do greatly influence industry decision on whether these compounds go forward.

I put down, first of all, regulatory, that the Pediatric Rule I think has made industry at least think about these studies, and hopefully, that translates into early implementation of pediatric studies. Again, the Pediatric Rule is early, I think we will get a better handle on whether that has really made an impact as we go forward.

I think when you look at the business development of these compounds, and looking at the potential impact of FDAMA and the Best Pharmaceuticals Act, exclusivity, I think again creates an environment within industry where they entertain the idea and think about these compounds going into a pediatric population much earlier than probably has ever been done in the past.

I think those factors on your left certainly influence industry to think about

implementing studies at an earlier stage in the development of a compound.

Now, what factors could actually influence a later entry into pediatric studies? Again, not being in industry for quite a few years, a lot of this was a surprise to me, but things as simple as CMC, chemistry manufacturing, formulation.

As we go into more and more oral agents, again, most of these agents are developed for adults. They capsule or tablet size, and most frequently, you will see capsules being developed before tablets being developed, and capsules are not obviously amenable to scoring and breaking into more pediatric-friendly dosage forms.

This will greatly I think influence when a lot of these oral compounds can go into pediatric populations. Again, we don't typically plan, I think at the earlier stage for pediatric dose size.

Stability, particularly for I.V. formulations. Most drugs, as they are first formulated, will go into vials, glass vials, which are single-entry vials. If you look at again the concentration of the drug in these vials, again, they are geared more towards the adult dosage form and adult dose.

So, when you go into pediatrics, if you need 5 mg of a drug and the vial comes in 50 mg sizes, if you go into that for an I.V. dose to be given, you end up wasting 80, 90 percent of the drug, which again I think dissuades against early pediatric studies.

Then, just simple drug supply. Again, something that has been brought up already, but something that I guess I didn't realize until really getting into industry, this is such a critical issue that is identified at a very early stage. It is not something that I would say is readily, or let's just make more drug.

It is much more difficult to make drug, to get it on stability, to get and release the correct formulation when it has been approved for release, that this is decided at a very early stage in the development of a drug, and to identify studies early on, particularly an interest for pediatric, I think is so critical in the development of these compounds, which can influence when these compounds go into pediatric study.

Lastly, I would say toxicology, unacceptable toxicities, clearly, industry is concerned with the development of compounds that

may result in unacceptable toxicities. How that is perceived by the public, how it is perceived by investors, how it is perceived even by the regulatory group, I think is a concern to industry, and that frequently results in some hesitancy to go into pediatric studies.

Then, unusual drug targets or unusual target organs, CNS, cardiac, renal, hepatic toxicities, I think all can be concerning enough to industry where it does shift some of the interest in early studies to develop those compounds more at a later stage.

[Slide.]

In summary, looking at more of a company perspective, I think there has clearly been shift towards really not if a drug should go into pediatric studies, but when it should go into pediatric studies.

I think you will see that these compounds will become more available, that there is a shift towards pediatric studies more and more. I think most pediatric oncologists believe that studies should be done early versus late. Company involvement is okay, but there is some caveats to that.

The perception at least is that conducting studies outside cooperative groups could speed up the process and that companies are showing increased interest in developing new agents in children.

I think this is a reflection, again, of several new legislative actions including FDAMA and the Pediatric Rule, that most factors that influence a decision to conduct studies in children is that the industry views I think are fairly similar to pediatric oncology views and needs, but there are clear, obvious differences between the two groups.

At that point, I guess I will stop and save questions and discussion for later.

DR. SANTANA: Thanks, Steve. That was a very good perspective from the other side--from the industry side, since I will be quoted in the minutes.

[Laughter.]

DR. SANTANA: I am going to invite Bruce to take his position at the podium and give us the European perspective of this issue, across the Atlantic now, right, the other, other side.

European Perspective

Bruce Morland, M.D.

DR. MORLAND: Thank you very much. I would like to thank the committee for giving me the opportunity to give you a European perspective of issues relating to new drug development.

What is already clear for me from the discussion and the talks is that the discussions that we are having in Europe are identical to the discussions that you are having today, and I could move this table to some committee room in Brussels, and we would be having exactly the same discussions.

I think another important factor that needs to be taken into account is that the pediatric oncology population is a truly international collaboration. One only needs to look at the results, the stunning results that have been achieved with national/international collaboration in Phase III trials to give a lead to the whole issue about Phase I or Phase II clinical trials being a truly international field, not just one that nations individually have to sort out.

So, I hope that this will just lead to further international collaboration and that we can help you along the way rather than us trying to do

it alongside you or separately from you.

[Slide.]

We have a number of challenges to face within Europe, and it is uncanny how many of the things I am going to say, Peter Adamson has already said, probably far more eloquently, as well.

But clearly, we, too, need to strive and are aiming to strive to access new drugs alongside and not after the adult Phase I/Phase II developments.

We have some new challenge in Europe relating to legislation, and in a typically modest European way, we have better, not best, better medicines for children, and that legislation is expected in 2004. It is clearly very important, it has some challenges for all of us.

A lot of our drug development has been in the area of academia, and there are some big challenges I think afoot to academic drug development programs certainly within the UK, and I think also throughout Europe, which means that a closer working relationship with the pharmaceutical industry is going to be essential.

Those issues relate to Good Clinical Practice, Good Manufacturing Practice, which means

that really even small biotech companies I think are going to find it challenging to actually manufacture drugs these days.

In the UK, we have this strange thing called the Doctors and Dentists Exemption, which is monitored by the Medicines Control Agency, but this allowed doctors and dentists with really very little preclinical data to bring drugs into clinical trials.

Now, I think with the new challenges that GCP are going to bring in, that exclusion is going to be really wiped out for us, and the academic drug development programs I think are potentially in jeopardy.

[Slide.]

Just a little geography lesson for you. The United Kingdom, this is a small island off the north coast of Europe. Some politicians would still like to maintain that island mentality, but we do actually have a tunnel that now joins the UK with mainland frogs, and I think certainly in the field of Phase I/Phase II drug developed for pediatrics, we have built very strong bridges across to mainland Europe, and I will explain some of those.

The United Kingdom Children's Cancer Study Group, UKCCSG, is I guess analogous to COG within the United States. We have 22 major centers treating childhood cancer within the United Kingdom.

[Slide.]

The organization has been founded for some 25 years. We celebrated our 25th anniversary this year. We have a large number of members, which are both treating pediatric oncologists, allied professionals, a very active nurses' group, et cetera, a number of overseas members, and unique I think in Europe is that we do have a centralized data office based in Leicester, which controls all of our trials activity.

[Slide.]

The New Agents Group of the UKCCSG was formed in '87, and has been primarily involved in Phase I and Phase II trials. We also did run the Relapse Registry, which was aiming to monitor those patients who were relapsing in order to get a feel of what proportion of UK patients were being offered Phase I or Phase II clinical trials.

In 1995, we established a very strong and now very robust link with the French group, SFOP,

and their pharmacology group.

[Slide.]

I am just going to whiz through a couple of slides just to list the New Agent Group studies that have been performed since its inception, and really to highlight again a point that I think Peter raised very importantly is that none of the agents that have been tested are particularly novel, new, or exciting, they are pretty conventional drugs, and they have largely been developed on the back of experience in adult practice.

[Slide.]

We have importantly developed a code of conduct for managing our clinical trials, and here listed are some key components of that code of conduct. Again, we did worry when we moved out into Europe as to how easy it would be to get clinical trials working across different cultures.

In fact, it has proved to be remarkably easy, and the barriers that are there are virtually nonexistent, and if they are there, they are extremely low barriers that you can hop over.

[Slide.]

There have been some issues about how long

it does take us to open a study, and I think when the pharmaceutical industry come to us with new agents, the whole issue about, well, it is taking an age to actually get through all of these processes, and it is not particularly attractive to us, is a real issue, but these are some of the steps.

I mean after some initial discussions in the group, we produce a protocol concept which goes to a wide UKCCSG meeting. In fact, what we used to then have to do is to take it to a second meeting to be finalized. As we only have two meetings a year, that automatically built in a six-month delay in initiating a study.

As Steven witnessed earlier this year, I was able to negotiate that we could actually remove one of these steps so we have shortened it somewhat.

We then had the ethical submissions, which in the UK now involves a national ethical submission, the so-called MREC for any studies involving more than five institutions. After the MREC submission has been approved, each individual hospital has to then submit also to its local ethical committee, and then you can open the study.

I think that that process never takes less than a year, and is often taking two years.

[Slide.]

In terms of the code of conduct with specific regard to Phase I studies, again, there are some key components to what we think should be doing, and I have to say not all of the 22 centers within the UK conduct Phase I studies.

We have restricted the number of Phase I centers, but clearly, the compromise is that we do reduce the number of eligible patients able to enter into our studies, but a lot of the issues relate to around staffing and particularly the need to have dedicated research nurse input.

[Slide.]

Similar code of conduct for Phase II studies, which again stresses the need for serious adverse event reporting and the importance of data monitoring and management.

[Slide.]

Just a few comments about the UK/French collaboration.

[Slide.]

We have now undertaken four joint studies with France, and that included a Phase II study of

temozolomide, a study of an agent called PSC833, which is a cyclosporine analogue, which was being used to reverse multi-drug resistance, daunoxome, liposomal daunorubicin, Phase I, and irinotecan, CPT-11, Phase II study.

[Slide.]

I am just going to use that CPT-11 study as an example, and again put some timelines along the development of this study, very similar to again Peter's presentation.

Here is the European development of CPT-11 in adult practice, which initiated Phase I studies in 1990 and went through to Phase II studies in 1992, U.S. licensing in 1996, and European approval was granted in 1997.

Well, let's just look and see where the pediatric development fits in here. It wasn't until Phase II adult studies were started to be undertaken that the company really released a drug for us to be able to undertake some preclinical xenograft studies, so they started early in 1992, and they were predominantly carried out by Gilles Vassal in Institut Gustave Roussy.

The French undertook a Phase I study, which recruited very quickly, but, in fact, the

reason that this is quite a long study is, in fact, the MTD was defined at a very significantly high dose level than the adult study. This is a single infusion every three weeks, so Peter would tell me we are using completely the wrong schedule here.

But the adult recommended dose is 350 mg, and the children's dose ended up being 600 mg/M2, so it was a very significant difference.

The joint Phase II study followed on immediately after that, and was completed earlier this year. So, if we look at the facts, it took seven years from initiation of the adult Phase I study before the first pediatric Phase I study in Europe was undertaken. Our goal is to do this in 18 months.

[Slide.]

Since the collaboration, the UK-French collaboration, I think we have done a lot, and between the two groups, and jointly, we have undertaken a reasonable number of studies, however, we have been very dependent on access to drugs from the pharmaceutical industry. If you think you have got problems with accessing numbers of agents in the United States, it is even more of an issue for us in Europe.

But I think the important factor to see here is that in a relatively short space of time, a significant number of patients, over 500 patients have been entered into Phase I and Phase II studies, but of all of these agents, all of them for us have been initiated after approval in adults.

[Slide.]

I just want to do some horizon scanning for you and give you what we hope will be the future in Europe, which is what we are calling the ITCC Project, Innovative Therapies for Children with Cancer, which is a really Integrated Pan European Clinical Research Network, which is designed to conduct comprehensive drug development programs in pediatric cancers, so this is true translational research. It is promoting fundamental basic science, preclinical modeling, and conduct of clinical trials.

[Slide.]

To that end, we have formed a core group of partners within the project - Institut Gustave Roussy in France, Cancer Research-UK, UKCCSG, New Agents Group, and the French Pharmacology Group, the Dutch New Agents Group, and the Germans have

joined us, too, and Joachim will give you some information about that very shortly, and the Italian group, as well, and the academic pharmaceutical input from the University of Newcastle.

It is by no means comprehensive, we also have input from the pharmaceutical industry, the EMEA obviously close partners with us, as well.

[Slide.]

But what is envisaged is that we have a network throughout Europe which is guiding drug development for pediatric oncology and linking both the academic institutions together, the pharmaceutical industries together, the clinical network, and also the regulatory authorities.

But as we all know, these networks are far from simple, there are very complex steps along the way, and once you actually start filling in all of these gaps, it becomes extraordinarily complex.

But if a network works, and I hope this one will, and there is no reason why it shouldn't, it shouldn't matter where you start in this network, there should be a one-stop shop for anyone wanting to undertake pharmaceutical studies in Europe, which says you phone ITCC, and they can

sort you out.

[Slide.]

So, let's just focus back on this timeline again. I think for us, the problems are way back here, and the issues are way back here, and one of my anxieties, and I don't know whether it is real because I have never been able to prove it, is what happens to the drug that is being developed usually by the pharmaceutical industry, that goes into a Phase I in adults, shows acceptable toxicity, then goes into adult Phase II data and because of lack of efficacy, the whole development program is halted.

Those drugs will probably never have been tested in a preclinical model of pediatric tumors, and certainly won't have been investigated in a Phase I study in children, and who knows what the activity that drug might have had in pediatric oncology.

Thank you.

DR. SANTANA: Thanks, Bruce.

Dr. Boos.

European Perspective

Joachim Boos, M.D.

DR. SANTANA: Do we have a computer

change?

DR. BOOS: Yes, but I can use the time to tell you one additional conflict of interest I had. We have currently autumn vacations in Germany, and my family is going to London and asked me to come with them, but I told them no, this is such an important meeting in the societies that interested in this point of discussion that I will go to Washington, and therefore, I thank you very much for the invitation and try to give you a short illustration on how the things work only in Germany.

[Slide.]

What do you see here? Nothing.

[Slide.]

But now you see here some of the representative tumor types in pediatric oncology, and they all happen in Germany, too. It is interesting for us that in a list of the HHO where they summarize the chemotherapy-sensitive tumor types, most of them are pediatric tumor types, only very few are adult tumor types.

If you look on the lists of what is labeled during the last years, all these yellow ones do not really, all these pediatric ones are

not on the list. Labeling normally goes to indications which are not primarily sensitive or not common in pediatrics.

This has two sides. First is immediately when they are on the market, and Peter Adamson told that they are used in pediatrics without any prevailing data, and the second is that in Germany, we currently are having very intense discussion in relation to the costs of the clinical treatment, and the health system is no longer willing to pay off-label for drugs.

This brings the whole pediatric oncology into a disaster, and it is therefore our major interest to come to more labeling for pediatric drugs, and not to increase the costs by academic ideas, but to speed up the process to make it as cheap as possible and as safe as necessary.

[Slide.]

In Germany, we have a cancer registry for childhood, and this registered all patients up to the age of 15, and we have roughly 1,800 new patients per year in the age under 15, and if we include the adolescent up to 18 or 20 years, we come up to roughly 2,400, 2,500 new patients a year.

All these patients are treated in cooperative treatment clinical trials, and you see here the indications and you see the trial groups, and it is the standard that there is one trial for the initial therapy and a second one for the relapse therapy, and with the second relapse, they are off study and on individual experimental therapy situations.

[Slide.]

These study groups have perhaps a bit Germany-specific role because there is a study committee and one coordinating center, and these centers are distributed all over Germany. In this map, I found Mnster was not included, therefore, I added it for you. Mnster is the green point. It is a bit bigger. This means not that it is more important, but we have the osteosarcoma trial, the Ewing's sarcoma trial, and the myeloid leukemia trial to organize for Germany.

Other centers have other tumor types. The centers are the principal investigators, not only responsible for the quality of the protocol for protocol writing, adverse event monitoring system, things like this, is, in addition, responsible for organizing the quality control, which means central

pathology refuse, central radiology refuse, central surgical planning, or things like this, and this is different than in many other countries, I think. There is an individual clinical consulting.

This means if any participating center has difficulties with an individual patient because of toxicity, because of unusual location of the tumor in question to the surgery, in all these situations, they phone to the center, and this is the experienced center for everything happening in this entity, and therefore, is sometimes in conflict between protocol compliance and patient's interests, and normally, then, you might expect, the patient's interests is the leading for the decisions.

Those protocols then are offered to the patients in roughly 80 to 100 centers, and in indications where the adolescents are included, up to 250. So, we have currently up to 250, but the core pediatric facilities are 80 to 100, and they treat between 10 and 120, 130 patients per year.

So, they need the experience of the center in individual situations. The aim is that patients do not have to drive too far to the hospital to where they are treated, but get the qualified and

standard therapy everywhere in Germany.

This means that if they come into a situation where they want to be part of the Phase I or II trial, we have to organize it that way, that they can still stay at home as long as possible, and they are not willing--or they are willing to go any center in the world or even on the moon, but if you have a new drug and cannot give them really a cure chance, then, we have the priority that the patients should be treated in the hospital that they are familiar with.

[Slide.]

The enrollment in the clinical trial system increased rapidly in the last years, and today, I think we are in the situation that more than 95 percent of the patients in Germany are really treated in these clinical trial organization, and this means from a statistical point of view, that this is not a subgroup with statistical probability. For Germany, at the end, the results of the trials describe the reality for the time the trial run.

[Slide.]

The results increased we saw in comparable presentation some time ago, increased from close to

zero up to in the mean 70 percent, five years survival, and when the physicians began with that, they were not enthusiastic that the drugs really could work. They only saw patients dying.

Now we know that these tumor entities have an interesting biology, have different biology, and are sensitive to chemotherapy, and I think we should continue with some enthusiasm and should try that the pharmaceutical industry shares this enthusiasm a bit more.

[Slide.]

So, if we have 2,000, 2,500 patients a year and 70 percent survivor, up to 700, 800 patients come into a situation where we can no longer offer them cure rates, they are palliative, and this is up to 50 percent leukemia, lymphoma, and to 50 percent solid tumors.

If we look only on specific tumor indications, like Ewing's sarcoma, for example, these numbers reduce significantly down to 20, sometimes 10 per indication per year in Germany, and this means we have to discuss when initiating a trial, is this really tumor-specific or is it more unspecific, is it really necessary to test a new drug in an indication like Ewing's sarcoma, or

would it be much more feasible just to focus on safety and look in solid pediatric tumors or embryoblastic pediatric tumors.

[Slide.]

This gives you a short impression on the strategy of the current Ewing's sarcoma protocol, and is one of the few situations where we could define therapeutic windows, and this is in the high risk group where we now define the therapeutic window, and in cooperation with the group Bruce Morland just mentioned, this therapeutic window, we are now filled with therapeutic or Phase II trials, which are discussed in the ITCC project on in the French, British, and in between European cooperative Phase I/II group.

[Slide.]

Then, this group can take access to an organization, which is European-wide, and I took the Ewing's sarcoma trial to show this to you. It is the adverse event monitoring strategy, reporting strategy in the Ewing's sarcoma trial, which is European-wide.

You see that the UK treats according to this protocol, France, Switzerland, Austria, Germany, The Netherlands. All these countries

contribute to this trial and have the regional or national committees, and the specific departments or clinicians report to the national committee, and the committee reports to the database in Leicester and to the database of the EORTC in Brussels.

Then, in Leicester and Brussels, all these data are summarized, and the information flows back, and the committees give it to the regional authorities and ethical committees, and what else.

This works fantastic and includes I think roughly 300 departments, I do not know exactly the number.

[Slide.]

But then we have to organize the trials in this way, that every department can be part of the trial, and in specific situations, especially when labeling is the aim of the process, we need some more GCP conformity and some more audits in specific centers, and things like this.

To provide a structural basis for such drugs, the German Ministry of Research and Technology some years ago initiated a program to sponsor coordinating centers for clinical trials, and those were seven centers for the first four years, and now again I think six or seven were

added, so that we up to now have roughly 13 centers in the universities in Germany, and 7 of those have specific coordinating centers for clinical trials in children, and this compares a little bit to the PPIUs in the U.S. and I think looked closely over the ocean when designing this application.

The coordinating center of clinical trials in Mnster now is responsible for organizing everything with pediatric oncology drug development for the society and for the KKS network.

[Slide.]

Before we define a specific tool I want to introduce to you, and this is in kind of roundtable, where we try to organize that everything is transparent to everybody and that we can catalyze the decisionmaking between the different social groups which are interested or not interested in drug development for children.

Therefore, our own society is at the table, the adult study groups are invited sometimes here, although generally, the pharmaceutical industry is invited to discuss with us, and then the regional authorities who have to check whether or not we work according to GOP and other things.

Then, we have the ethical committees

involved, one or two lawyers, and representatives of the patient groups, and discuss then the value of the preclinical data. This is normally an interesting, but not very helpful discussion.

Then, we discuss the priority of the drugs. This would be a fine situation, but normally does not happen because we do not have enough drugs for 700 or 800 patients who really ask us to be part of experimental treatment.

Then, we discuss whether or not it is necessary to develop a pediatric formulation, and in cooperation with our pharmaceutical technology, we have I think really a lot of experience to discuss this point, and sometimes it would be very helpful if, in the early discussions on pharmaceutical preparations, the companies would ask more to pediatricians or pediatric pharmacists because the choice of solubilizers or other necessary stuff could make things easier for us later on if you avoid benzyl alcohol or DMA or things like this.

This, we discuss trials, the financial aspects, the ethical problems, the GCP compromises, because compromises are always necessary in pediatric multicenter trials, and then we discuss

what this KKS can be supportive for the trial, writing protocols or something like this, everything we can do that the interested investigator has less work, then speeds up the process.

So, this is a kind of catalyzer between industry, authorities, and investigators to enhance quality and to enhance the time frame, because the question of the patients is to hurry up, they are waiting for these drugs.

Then, we define the network of 15 pediatric oncology centers cooperating with KKS, and these 15 represent roughly half of the patient numbers in Germany, so those are the bigger centers with more than 50 patients per year. They have contracts that they follow the SOPs and the GCP guidelines, and things like this.

[Slide.]

This all is more prospectively enthusiastic than we could fill it in the past with data, so a Phase I has never been done. I only remember one in Germany. This was on MTGD-1 some years ago, the only one I remember.

There are several Phase II-like trials in the Clinical Trial Groups, but this is offering

more less experimental therapy in first or second relapse.

We currently, by the system of KKS, initiated some trials which is IV busulfan, two trials with gencitabine, one with asparaginase, and one with topotecan/carboplatinum. Those are only drugs which are long known on the market, and there is no trial with a complete sponsoring by the industry.

We are interested in changing this. We are not primarily interested in running Phase I trials. If there is capacity and much more experienced groups, there is no necessity for us to spend time on Phase I trials, but we are now in the situation that we can contribute to Phase I trials if other groups need patients to speed up the result generation.

[Slide.]

The questions are always the same in these roundtables between industry and others, what is the preclinical marker indicating priority, okay, we discussed that. What is realistically an indication, what do we look for. This is a very important issue from my point of view.

What are the realistic endpoints in second

or third relapse? Response, probably not. What is a realistic level of significance if you focus on Ewing's sarcoma and have only 20 patients a year, can you really expect 0.5, is it really necessary, and what is the power you need?

Every compromise here is much better than standard off-label use worldwide.

[Slide.]

Some very short words on preclinical screening because we just organized this pattern of roughly 15 cell lines representing all the pediatric tumor types, and there is no necessity to go on this in detail.

We first tested in four Ewing's sarcoma cells lines, gemcitabine, an old drug we were rather interested in, and it is on the market since five or six years, and never been systematically investigated in children, and could expand the indication in the adult area year by year, so we were interested in this and saw very good preclinical data in these MTTSAs.

[Slide.]

We compared it to a very new drug mentioned here sometimes today, which is Gleevec, Ewing's sarcoma express c-kit and PDGF, and all

these cell lines did it, but they were non-responsive in this in vitro testing, and therefore this was the first time we had decided to continue with gemcitabine, not with Gleevec, and a little bit in doubt whether this is really a sound basis for such a decision, but if I were a patient, I would prefer gemcitabine, not Gleevec after such results.

Thank you very much.

Committee Discussion

DR. SANTANA: Thank you, Dr. Boos.

One thing that occurred to me as I was listening to these presentations from the European perspective and the industry perspective that I think hopefully--Malcolm may want to comment on this--will be addressed in this national U.S. effort to establish preclinical models is the issue of standardization, and clearly are characterizing these models, so that when they are tested against different drugs, we are really looking at the same thing, and we are not trying to make judgments on potential activity when different groups are using different models that have not been adequately standardized.

So, that is just an editorial comment, but

it occurred to me as I was listening to some of these presentations that if industry is going to use different models than we are going to use in the consortium, that the NCI may use, we are going to set ourselves into a big problem, we are not really going to be able to use these models very effectively.

Do you want to comment on that, Malcolm?

DR. SMITH: I will just say as background our efforts in this area were really given a boost by a meeting that we sponsored in June of last year, getting a group of experts in preclinical testing together to talk about this challenge.

Out of that meeting there was a sense of enthusiasm for proceeding with an effort in this area. The schema that Peter Houghton showed actually came out of that meeting.

As that schema indicates, what we envision is a panel of xenografts that are well characterized in terms of their biological characteristics and that are used repetitively to test each of the agents that come through the preclinical system, so that we do get an experience with the same group of tumors and can then make both the retrospective correlation, then, the

prospective correlations between the preclinical patterns of activity and the clinical patterns of activity.

So, we are actively pursuing ways to support such an activity.

DR. ADAMSON: I have actually a number of comments that I will try to tie together under one theme and to try to address at least one question that I think is an important question that Steve proposed.

The theme of my response is going to be the importance of communication, and that is communication both nationally, internationally between academia, industry, and the cooperative groups.

As far as whether should the cooperative group be the only venue for pediatric cancer drug development at least in Phase I, my answer is no, it should not be the only venue. Having said that, let me expand upon why I think it is a critically important and productive venue.

The new COG Phase I consortium actually just started receiving funding in July of this year, so it is truly a new entity. Susan Blaney and I co-chaired that committee and we have also

had the experience of working directly with industry on a number of non-oncologic pediatric drug development and have a very good sense of what industry timelines really are versus what academic timelines are and cooperative group timelines are.

Although we have a productive cooperative group, we do not believe our timelines yet are where they should be. They are simply not at the level of efficiency that we are demanding of them, and certainly not at the level of efficiency that industry would demand of them.

We have put in place a number of standard operating procedures and are actively addressing where we think the inefficiencies are. Our goal, and I think it is a realistic goal, is that our cooperative group will be the most productive, efficient venue for industry when developing new cancer drugs for children.

With that in mind, what we can give to industry is it is really a remarkable resource with an infrastructure already in place with the pediatric expertise at major centers in place, but monopolies, in my opinion, are never good, be it Microsoft or be it other monopolies.

I certainly think that there are centers

in the United States that have demonstrated the ability to carry out these trials. St. Jude is an excellent example, the Pediatric Oncology Branch at the NCI is an example, and there are likely to be other examples.

So, I don't think industry has to come to the cooperative group in order to develop the trial, but what is critical is that we communicate, because doing the Phase I trial, quite honestly, is easy.

What is harder is the development plan for the agent, and that development plan ultimately should be looking towards Phase III. At Phase III, one has to utilize the cooperative group in pediatrics.

So, to set out to do a Phase I without ever communicating with the cooperative group, I think is counterproductive. That is not a good utilization of resources.

I don't think we should be the only place to do Phase I's, but we ought to know about Phase I's that are occurring, and discussions ought to take place with, well, how will we develop this beyond Phase I.

If those discussions do not take place

because industry is operating outside the cooperative group with certain institutions, then, I think we are doing a disservice to overall drug development in children.

Industry, I think has an important role to play, and certainly bringing resources to the drug development process can always improve the efficiency upon systems, so the cooperative group mechanisms, which has resources, does not have sufficient resources to leap the gap that occurs when doing a fully industry-funded trial from one that is funded only by the NCI.

The key point, however, is we need to communicate about this. We do not want to find ourselves in the situation that especially when it comes to analogues or me-too drugs that trials are being done only with pediatric exclusivity in mind, and not with long-term development plans.

DR. SANTANA: Dave.

DR. POPLACK: I just want to follow up on two points made by the speakers. The first is in response to Joachim's figure of the child and the denotation of the need for us to hurry up, but basically to emphasize the point that Peter Adamson made regarding.

We are in a doubly ironic situation, because we have been so successful, we have fewer patients available for Phase I studies, and yet also we are at a time when we have so many more agents potentially available, but we can't get access to those agents.

I really think, and hopefully, the advocates in the room will hear this clearly, that we are at a crisis point, we really have to do something in some way to influence government policy to make certain that access to these agents is provided to institutions and groups involved in studying these agents.

I don't think it is very helpful, frankly, to come in and listen to comments, and not to single you out, Steve, but from the other side, that use issues such as formulation problems as being the mitigating circumstance that delays development in pediatrics. It is a bogus issue.

I think the other issues that are out there are economic issues, and those are the ones that have to be dealt with in the spirit of cooperation. I know that the representatives in this room from industry, many of whom are pediatric oncologists and feel equally deeply as we do, the

need to move the system along.

We have to I think look to changes in policy and perhaps incentives first to make it easy for companies and advantageous for them to provide us access to these agents.

The other point I want to emphasize was alluded to by Peter, and that is, it is important to allow single institutions or groups perhaps other than the COG to be able to do Phase I studies, but the big caveat is, is that things need to be organized and prioritized because we can't allow pediatric oncology to persist in repeating the history of our past, which has been somewhat checkered in terms of doing analogue studies in which individual institutions fall prey to economic pressures to do a study of an agent that is an analogue study, because those patients then get truly lost to studies that could be much more important, of drugs with new mechanisms of action, for example.

DR. SANTANA: Jerry.

DR. FINKLESTEIN: I do not want to preempt the next series of speakers, but I would like to give a quick historical basis.

In February 2000, that is over two years

ago, I had the opportunity to co-chair a meeting, some of the people in this room were there, representatives of FDA, NCI, the cooperative groups, the public, the American Academy of Pediatrics, and industry, and our topic was, as Peter pointed out, drug availability for children with cancer.

I congratulated the FDA at that time, and I congratulate them now, because Mack Lumpkin, who really came up after a little meeting in a side room with a process that actually ended up with the institution of this committee. So, the FDA has taken a tremendous lead.

Drug availability in February 2000 has yet to be solved, and we are already in October 2000, we have made very little progress. I would like to reemphasize what David just said.

What we need from everyone is a change in behavior, and thus far, and I apologize, I was called out for part of your talk, thus far, I have not seen or heard in the last two and a half years any significant change in behavior by all individuals who address the problem of pediatric cancer and drug availability.

So, I look forward to the next series of

speakers whose topics are supposed to be identifying and overcoming barriers, and if we don't have the answers then, then, I believe it is the role of this committee to sit down and just drag out the issues, one by one, and create an algorithm which will change behavior.

DR. OCHS: Hi. Judy Ochs from AstraZeneca.

I was 20 years an pediatric oncologist, and I might add that in my company, on the Iressa or ZD1839 program, we have a token medical oncologist. The four lead physicians are pediatric oncologists. So, you already have a voice in many of the companies, you really do.

There are several things that occurred to me listening to this presentation. The whole first part of your presentation focused on classic cytotoxic drug development.

If you look at what is currently in the pipeline in most companies, all of the drugs, I saw a recent pie diagram, 15 percent are cytotoxics, and the other 85 percent are Other, whether they are novel agents, monoclonal antibodies, et cetera, so you have to be geared up to test these other agents, too.

The other thing is that when you look at Phase I agents, a lot of these novel drugs are going to have novel targets. Iressa or ZD1839, we do have three pediatric trials, and they were started, and they were started rapidly, and a large part of the reason was Peter Houghton, because Peter not only had the xenograft model, but he also had data to show that the target was present in certain pediatric tumors, so we were able to go and do that very quickly and start discussions.

In fact, we started discussions with both St. Jude and the cooperative groups while we were still doing the Phase I in adults. I would also say if you want to do Phase I trials in children, at the very end of Phase I of trials in adults or at the same time, then, you are going to have to be committed to work very closely with the company because the company's key priority is safety, and they are particularly anxious about safety in children, as other people are on the outside of pediatric oncology.

When we ran the Phase I program with Iressa, which preclinically, our toxicology showed was an extremely safe agent, we had weekly telecons with all the investigators. So, again, it is a

certain level of commitment on the cooperative group part.

I would also state that I think that the major of the trials should be done in the cooperative groups, and of the three pediatric trials we have, one is with the cooperative group, one is with the Pediatric Brain Tumor Consortium, and one is with St. Jude, and that also reflects the fact that there are certain needs that companies may have for certain drugs that can't be done in a cooperative group mechanism.

Part of the reason we went to St. Jude was Peter Houghton and his data. The other reason was it was a single institution, and at that time we were concerned about eye toxicity. We had a single institution which could perform serial studies. So, a lot of these targeted agents are going to have very specific needs that not all the time a cooperative group can take care of.

Lastly, there is the time factor. I think right now you have a tremendous carrot. You have a tremendous carrot, which is the pediatric exclusivity, and most of the companies want to work with you, but again, if you are going to be looking at some of these newer agents, you need to rethink

some of the things you are doing.

We are grappling with how to do good clinical trial designs in these agents as it is, and it is a bit tougher in pediatrics in some ways, but again, you have a tremendous carrot. The companies are more than willing, but if you have a novel agent, you have to show us that you have the target present.

I would agree also that I don't like the term "targeted." I think it is biologically based as we are trying to figure out what the exact target is in some of these things.

DR. PRZEPIORKA: A question for Dr. Hirschfeld or Dr. Pazdur. I was surprised not to see someone from the FDA speaking on the list this morning. The reason I say that is because we have heard a lot today about the access to barrier to drug, and that is clearly true if you were getting your drug from a pharmaceutical company.

We have heard in the past a lot about the development plan and the pathway to registration, but many of the pediatric malignancies are truly orphan diseases, and if you really want to get to the point of a randomized trial, it may take decades, and yet there may be some drugs out there

which someone wishes to study.

They could get the drug by making it themselves nowadays now that academics have their own GMP facilities.

How will you view individuals who come to you with INDs to do studies with no clear pathway for registration, and obviously, in a population so small that no company wants to take it up because of economic problems?

DR. HIRSCHFELD: I was counting on the legacy of our previous meetings to make some of the points, and didn't want to take up time reviewing things which we have done before, but weave it into the conversation.

So, I will take this opportunity to point out that we have issued about 30 written requests, and about half of them are for approved drugs, so anyone that does the math realizes that the rest are for investigational agents, and there is enormous interest in activity in pursuing programs.

With regard to having a requirement that someone have a complete development plan, we don't have the mandate to do that, but we always ask that question, and our pediatric written requests just to discuss one aspect of our programs, not the

entire aspect, begin with an introductory paragraph which emphasizes the need, first, for an entire development plan, and, second, for a pediatric development plan.

So, we have put this in the fabric of our interactions with sponsors whether they are industry or otherwise for about at least two years, as Dr. Finklestein pointed out, and I am going to defer to Dr. Pazdur just to discuss our mention, our interest and emphasis on having an overall development plan.

DR. PAZDUR: I think, number one, drug development is a stepwise basis, and when somebody comes in to us with their first Phase I drug study, they are not going to have a complete development plan because for traditional agents, more or less, they have been looking at hints of activity.

We could talk all we want about targeted therapies, but many times people are looking at what are the initial glimmers of activity and if that tumor has activity or one sees activity in that tumor, then, that sometimes guides the pathway.

We are asking sponsors to really concentrate on more of a development plan rather

than just coming to us with individual protocols. That is part of our end of Phase II meeting to discuss with them where they are going.

With our development of accelerated approval, for example, where many of our drugs are getting their initial approval, we want to have in place a development plan of where they are going to show clinical benefit even before we approve some of these drugs. That has to be in place.

So, the development plan is something that evolves. Initially, we are not going to have it, especially at the time where many of you people want to have these drugs going into pediatric drug development, it is simply not there.

There is a lot of talk about barriers to drug development and how tumors are selected--or not tumors, but the selection of a development plan, and I still think no matter how sophisticated our models may be, the biggest encouragement for companies to invest in a drug is to see that initial glimmer of activity in a Phase I study.

That is far more important than any alleged theoretical mechanism of action here, and that will basically dictate a lot of where they are willing to put their money as far as developing a

drug in pediatrics because you have to understand that it is a financial expenditure that they are making here. That is what guides many of this.

We have very little regulatory authority over that, nevertheless.

DR. WEITMAN: I just want to comment on a couple of things, and I will echo a little bit what Judy said. Again, I don't want to be, you know, this side at least of the room be viewed as adversaries.

DR. SANTANA: I completely retract that comment.

DR. WEITMAN: We are all pediatric focused and have an interest, otherwise, we wouldn't be here today.

Clearly, I share a lot of the frustrations with availability of drug having been in the shoes of Peter and others here, begging for drugs. I remember working with Charley Pratt trying to get gemcitabine, and that was such a frustrating experience. I think we all realize that availability is important.

I do want to echo a couple of statements. I think certainly communication is important. I think once the drugs from what I can see get into

adult Phase I, and there is that glimmer of hope in Phase I, where there is a commitment all of a sudden on the company to take that compound forward into multiple Phase II studies, at that point, the clinical development plans begin to be set.

With that, that sets the number of studies based on how much drug has already been made or will be made. It does set the study populations. It does set to a certain extent the formulation, and again I am not implying that formulation prevents studies, but it clearly helps determine what capsule sizes are made, and so forth.

I would echo the need for communication, and I would say when it comes to the end of Phase I, the start of Phase II, when those clinical development plans are being set, that is from what I can see the best time for this communication to start. I wouldn't say not at IND time, but once there is a commitment to go ahead with the Phase II because there is activity, enough in the Phase I to want to see that compound developed, that is when prior to really formulating the budgets around the clinical development plan, the numbers of studies which dictates how much drug is made, that is when really the communication within the pediatric

community really needs to be undertaken.

DR. SANTANA: Steve, let me just comment on that briefly. I think the issue of access in part has focused a little bit on the clinical access to the studies, but there is another side to that coin.

It is the access of the drug much earlier, so that individuals who have an interest in testing it in models can have very early access to the drug, so we can determine very early on whether we have an interest even before we even get to the issue of discussing Phase I and II trials.

DR. WEITMAN: I don't think that really should be any barrier there at all.

DR. SANTANA: It is an issue.

DR. WEITMAN: It is an issue, but I would agree, I don't think it should be and particularly if non-GLP material is required, for most of these studies it is not, and it shouldn't be an issue. Maybe that's at pre-IND state when that can be discussed.

DR. ADAMSON: Just to pick up on that last point, Steve, I think, and Peter can probably comment on this better than I, it has been a critically limiting issue for preclinical

development, trying to get these agents into preclinical studies, and what we are looking towards as far as our screening consortium is that when strong consideration is being made to move a drug into Phase I in adults, adult Phase I's, certainly no later than what it already is in adult Phase I's, that is when we want the agent to come into our consortium, so that by the time it is nearing the end of adult Phase I, we actually have some data to tell us is there a pediatric rationale to move this forward.

Now, to come back a little bit to what Judy was saying, Iressa, in fact, I think was a good example, but it was a rare example, and I also think that the carrot, we have yet to see if this carrot of pediatric exclusivity is going to truly be relevant for early cancer drug development.

Much of industry gets interested toward the end of the life cycle as far as what the true value of exclusivity is, and a lot of times exclusivity is not even being discussed when a drug is just entering Phase I.

So, there may, in fact, need to be, as Jerry and Dave have pointed out, a change in behavior, a change in outlook. Perhaps an

incentive of the preclinical studies is not only the positive data that may emerge saying yes, we want to move it into pediatrics, but there may be value to negative data saying that this is not an agent that is, in fact, we believe relevant based on the knowledge we have to move forward, and a company could hopefully use that information to say, okay, this was our, you know, attempt if we wanted to move it forward in pediatric, to meet our obligations, not exclusivity, but just to meet the pediatric drug development plan, however, there is sufficient evidence here that it is not relevant to this disease entity.

Lastly, coming back to the point about cooperative groups, our Phase I consortium is flexible and that we recognize that it is not always appropriate or necessary to study a drug in 21 institutions, and when there is a rational reason not to do so, we have the flexibility not to do that and to study in a smaller number.

We also have the flexibility to bring in other institutions that, in fact, bring expertise that we don't have.

Having said all that, I still stand by my earlier statement that there are going to be

occasions that, in fact, it is better and more efficient to do it outside the cooperative group.

I envision that those will be fewer and less common as we move forward, but they will always be there, and the key is communicating with the cooperative group as far as what is in early development.

DR. REYNOLDS: I just want to echo the comments by Vic and Peter that the access of these drugs for preclinical testing is an absolute disaster, to use a strong term for those of us that are trying to do this.

We are averaging two years to try and get an MTA through to get this, and that sometimes it takes as much as two or three years just to get them to send an MTA from the company. I have one case--I won't mention the drug and company--in which there were 17 e-mails over a two-year span, and the only way I was able to get an MTA is thanks to Malcolm's people stepping in from the NCI and finally getting an MTA through.

So, I bring this also up in the context of your earlier question, Steve, as to what the timing would be in terms of generating preclinical data.

I can tell you that the timing is mostly

not impacted by the time it takes to do the experiments, but 10 times as long as it has taken in trying to deal with the lawyers, and we have to come to grips with that and come up with a way where industry can work hopefully through the NCI, as Malcolm has been trying to do, over the standard MTA, that all the academic institutions participating in this can sign off on and that one MTA, they don't have to re-read it again, because it is standard, and if we can get through that point, that will be a major accomplishment and will really help this forward.

DR. WEITMAN: One quick comment. I think at the time of IND submission really I think would be a critical time to look at some mechanism at that point when drug can be made available for these studies, because again I think that is early enough to give the pediatric community, the research community, the chance to get the drug to do their studies that they need, so by the time the adult Phase I studies are nearing completion, you know, or even before that, the results would be available from those studies.

I know there may not be any regulatory way of doing that, but I think that, to me, would be an

ideal time point and when to trigger providing drug for studies.

DR. SANTANA: We are going to have time to follow up on this discussion because a lot of the session that we had planned for this morning was actually going to try to address some of these issues.

For the sake of time, I am going to ask that we take about a five-minute break and then we are going to try to come back and finish the next three presentations, and then we will do our lunch break.

[Recess.]

Identifying and Overcoming Barriers

Children's Oncology Group Perspective

Gregory Reaman, M.D.

DR. SANTANA: First, is a discussion of identifying barriers and how we could overcome those. We are going to have Dr. Reaman from the Children's Oncology Group give the first presentation.

Greg, please.

DR. REAMAN: Thanks very much, Victor. It is a pleasure to be here and it is a particular pleasure to be representing the monolith in this

whole spectrum of pediatric oncology drug development.

As I heard that word, which obviously I find a little bit difficult, I am reminded that I have always had the association of cooperative groups being monolithic, but since we have merged and become a single pediatric cooperative group, I can't even imagine the perception that people must, incorrectly of course, have of us out there.

Although we are not a monolith, I think we do have some operational inefficiencies. I am not sure that they are really inefficiencies. I think we have some operational disasters. Many of them are, in fact, because of the fact that we are severely resource limited, we recognize those operational problems, we are dealing with them as rapidly as we can, and I think the pediatric cooperative group is the best place to do new drug testing in pediatric cancer.

We, too, like industry, are very concerned about safety, safety in children. We basically exist or have existed for the last 45 years trying to prevent children from dying from cancer, so safety is a big concern of ours, as well. It basically drives all of the clinical trials that we

do.

[Slide.]

The barriers. There are just a few and a lot of this will be repetitive, so I am going to move through it pretty rapidly.

What we see as a cooperative group as barriers to new drug development are basically 3-fold - the market forces and economic forces that make drugs available for pediatric cancer, the current testing of new drugs in children, and the shifting paradigm, and it continues to shift and has been shifting for the last 10 years.

The legislation and regulations which impact or influence drug testing in pediatric cancer, all of which initially began as a way of protecting the interests of children and guaranteeing their safety, and are they really a help or are they a hindrance, the difficulties with interpretation and the difference in perception among various interest group create problems for us, as well.

The solution is really very simple, and it basically boils down to communication, which has already been raised, and communication and early communication, and it is hard to imagine, Jerry,

that the meeting that we had with the FDA and the American Academy of Pediatrics was only two years ago. I thought it was four or five years ago, but time flies when you are having a good time.

But I think that communication will certainly result in coordination which we really need.

[Slide.]

As far as market forces, cancer is not a common disease in the pediatric age group, and has been touted to only be 3 percent of the cancer problem.

Patent exclusivity is also not the carrot that one would imagine that it could be, and the whole drive to label drugs with indications in pediatric cancer is not a particular carrot for practicing oncologists who are very used to using approved drugs off-label as either single agents or in combinations for the treatment of pediatric cancer and for the clinical trials in pediatric cancer.

The problem is further complicated by the fact that pretty much the standard of care in pediatric cancer management is done within the context of academic centers and in large part

within the context of participation in clinical trials.

The provider audience for the pharmaceutical industry is relatively limited and confined, as well.

[Slide.]

As far as other barriers, there are certainly limited subjects for clinical trials, and we are happy about that to some extent. We are victims of our own success.

Although we may have limited subjects for the development of new drugs for new indications for new diseases that are refractory to current therapies, we certainly have an equal obligation to find less toxic and safer drugs that are just as effective as currently available therapies.

There is a requirement for the most part for multicenter studies with the exception of a handful of programs. In this country, most new drug testing requires the participation of multiple institutions working together.

Another barrier includes the correlative studies which are required in pediatric new drug testing including pharmacokinetics, pharmacodynamics, and an increasing desire to do

pharmacogenic studies, as well, and obviously ethical considerations in testing new drugs, new agents in children, the first ensuring that there is human proof of principle, are we testing new drugs in children for a potential therapeutic benefit in that child or are we evaluating maximum tolerated dose, potential pediatric dose-limiting toxicities.

And then, of course, the issue of assent for participation in clinical trials in general, but specifically in new agent testing in minors.

[Slide.]

As far as the shifting paradigm, the timing of pediatric studies relative to adult trials is very critical, and I would certainly agree with Peter's statement that the only thing that drove pediatric Phase I studies in the past was the availability of a new agent.

I would soften that a little bit in that we didn't always move those new agents forward only because of their availability, and we were also burned on many occasions testing drugs in the Phase I setting, and being very excited about them, only to find out that since the drug was inactive in breast or colon cancer, it wasn't going to be

developed any further by the industry.

Early adult toxicity data, I think is critical, early adult efficacy data, less critical, and the whole issue of how we now assess responses and particularly assess responses in clinical trials involving agents with novel mechanisms of action.

[Slide.]

We also have to look at how we proceed from Phase I and PK studies in the pediatric age group - do we automatically go to broad-based Phase II studies looking at efficacy in all of pediatric cancer, or do we do this in targeted disease groups, is refractory disease the only place to evaluate new agents in children, or is there a role for early evaluation in Phase II settings in particular patient populations.

Obviously, the concern, as in most cancers, we don't treat with single agents, the role of combination studies.

[Slide.]

As far as molecularly targeted therapy, validation of suspect targets in pediatric tumors, we see as a potential barrier and one that is rapidly being overcome. We look forward to the

fact that many of these agents, which are biologically or molecularly targeted, have relatively favorable toxicity profiles.

We would like to assure that pediatric studies are in the agent's development timeline, so the early validation of suspect targets and the early inclusion of consideration of pediatric cancer is important in the development plan.

Response assessment, we see as potentially difficult in the pediatric age group as we look at new trial designs looking at surrogate endpoints utilizing perhaps imaging as a technique, sometimes including tissue responses requiring repeated biopsies, and is that something that is actually going to be feasible in the pediatric age group.

As far as legislation and regulations, we have the fear that we are coming to a feast or famine situation, and it is actually from a famine to feast situation, and that in the past, despite our pleas, it took five to seven to 10 years to gain access to an agent, and now we may have too many agents to test.

This really needs to be carefully evaluated with incentivization plans, and how is that going to really fit with disease-specific drug

development plans, and particularly when mandated pediatric testing looms on the horizon, and how is that testing actually going to fit into disease-specific, pediatric cancer-specific treatment strategies.

I would again plead that there has to be early communication and coordination with the pediatric cooperative group if not solely on the basis of new agent testing, but where is that new agent going to fit in the scientific agenda of a particular disease treatment plan.

I look to this subcommittee to really help in the definition of indication and substantial benefit in pediatric patients.

[Slide.]

Obviously, communication is important, coordination, so that rational prioritization can proceed is vitally important. The timing of adult and pediatric studies, should they be sequential, can they be simultaneous, do we have to have adult MTDs, do we have to have evidence of biologic effect.

We need to have some evidence, and I think that evidence needs to be agent-specific, and we probably don't need a hard and fast rule.

We do need to increase our efforts at validating potential molecular targets in pediatric tumors and work closely with the preclinical assessment and the consortium that has been already discussed.

Translating those findings to clinical trials will be vitally important, and obviously making sure that consistent drug source and supply is going to be there for the pediatric population.

[Slide.]

Again, the therapy plans and even for targeted therapy plans really need to be disease specific.

The other place where I think we need to definitely communicate and coordinate and collaborate is globally and internationally. Given the very limited patient population resource that we have, we can't duplicate studies of the same agent or analogues of agents in patient populations.

We really can't do that, and I think we can have greatly enhanced opportunities for targeted Phase II studies in combination trials by working together internationally.

Thanks.

DR. SANTANA: Thanks. We will have opportunities for questions and comments later on.

I am going to invite Barry Anderson from the NCI to give comments related to the NCI perspective.

National Cancer Institute Perspective

Barry Anderson, M.D., Ph.D.

DR. ANDERSON: I want to thank Steven and Victor and give some points from the NCI about issues that we see as being important to be maintained and other barriers and challenges to be overcome, to foster a Phase I approach to pediatric oncology drug development in North America and the U.S.

[Slide.]

The first would be a point of infrastructure for actually being able to perform these studies, and as Peter Adamson has mentioned already, the COG Phase I pilot consortia, which now consists of 21 institutions, was reconstituted with the fusion of CCG and in COG institutions together, and they currently have a host of Phase I trials open and a number of new agent studies that should be opening soon.

Another consortium that I think someone

else has mentioned today is the Pediatric Brain Tumor Consortium, and this was initiated in 1999. It consists of 10 institutions now.

It has a number of Phase I institutions and studying therapies that are focused on not just new drugs, but new surgical approaches and radiation therapy strategies for children with CNS tumors.

[Slide.]

Outside of these larger groups, Peter Houghton has his PO1 grant at St. Jude Children's Research Hospital for the study of new agents in solid tumors, and as Pat Reynolds has mentioned, there is a program project grant that is held by Robert Seiger [ph] at Children's Hospital of L.A. for new approaches to neuroblastoma treatment or the NANT.

This is I believe 12 institutions that is working together to look at new therapies focused on high-risk neuroblastoma, and they currently have four, Phase I trials and some Phase II trials open.

Again, there is also the Intramural Program at the NCI Pediatric Oncology Branch, which can do Phase I studies independently, but also cooperates with the COG Phase I institutions.

[Slide.]

People have talked about prioritization of agents because of the plethora of new agents that we all read about and that we all hear about being studied in the adult clinics. We always will have a limited and shrinking number of patients available. We realize that many agents will never be studied and we have to make choices, so future progress in drug development in pediatrics is going to depend on trying to pick the right agents.

[Slide.]

This dated list of anti-VEGF agents shows you that if we can only pick one or two, because that's how many patients we have available, we have to be smarter about how we do that.

[Slide.]

So, the pediatric preclinical testing program that Peter Houghton has spoken about earlier has been something that we at NCI have been working on for the past year and a half.

The goal would be to help prioritize among the available new agents. We are hopeful, with the information that Dr. Houghton has provided, that these models can be predictive, and efforts are underway right now to establish, one, a coordinated

structure; two, that what testing procedures will be important to have is sort of a standard system to bring new agents through.

We recently had a meeting between sponsors and investigators to talk about the legal agreements that will be necessary both on the institutional level, as well as on the pharmaceutical sponsor level and the NCI level, and for what Pat Reynolds had brought up.

We are working on a model MTA that was presented during this meeting, discussed with lawyers that came from the pharmaceutical sponsors, NCI lawyers, lawyers from tech transfer groups within the institutions, and we now have gotten comments on that from a number of the institutions and the pharmaceutical companies, will send out sort of the next iteration of that and then kind of go on a broader scale, so we are hopeful that that will be a means to bring drugs that are actually early on in the pipeline at pharmaceutical companies to preclinical testing.

[Slide.]

Next, the topic of access to new agents. There is two components to that. In terms of access from the sponsors, we all know about the

financial disincentives that there is to a sponsor to actually study a new agent in the small population of pediatric oncology and that often pediatrics is outside the drug development plan.

I think the changes that have been made at the FDA, as well as the push from the patient advocates and from the COG has helped to influence these components somewhat. The limited drug supply remains a factor.

We hear about that at CTEP when we have an agent that we are trying to help a drug company to develop. Oftentimes, because CTEP has a series of studies it wants to do, we have to advocate for setting some drug aside for pediatrics, as well, and often until there is some greater impetus behind that in terms of activity found, we still have to wait even with drugs that we see coming we think that CTEP has access to.

Perceived risks of doing studies will always be there I think from the pharmaceutical industry point of view, and the question of how much need to demonstrate activity in adult patients before you go into pediatrics is something that has been discussed.

Another component of that is need for

correlative study information in targeted or biologically-based agent development, and that is something that we will mention in a second.

[Slide.]

Another part of access to agents is from the patients' perspective. There has been some discussion as the number of institutions within the Phase I consortium has changed, about how do we get access to everybody because everybody needs to get access to Phase I studies.

Well, we don't really think that Phase I trials are the way to get access to agents necessarily for all the patients who might want those. By the sheer nature of a Phase I study, there is frequent study closures, there is just a few patients that are ever going to be enrolled, and as Peter mentioned, the waiting list lotteries that are on hand whenever a particularly hot drug hits the media and everybody's attention.

We feel it is actually better to speed up or facilitate the Phase I component of drug development, so that you have a better access through Phase II trials and pilot studies that can be open nationwide, and don't require quite the special attention that you have for Phase I

studies.

Also, in very special situations, the special exception programs can be activated either through the NCI or by industry until a study is available.

[Slide.]

Now, in terms of the appropriate timing of Phase I study initiative in pediatrics, when the endpoint is MTD, so that would apply mostly to cytotoxic agents as people have mentioned, we feel that upon determination of the adult recommended Phase II dose, that is when you should be able to open the Phase I study for pediatrics.

That means that the study has already been proposed, it has already been perhaps approved maybe without the dose level that you are going to start out on, but that you should have that much information from adults beforehand, pragmatic reasons, again, because of the limited number of patients we have in pediatrics, but also to avoid those agents that would fail early phase adult trials.

I can tell you that a number of groups, people have called us. They have done in vitro studies, they have done preclinical studies, and

the drug disappears as it is going into the Phase II in adults, and everybody is like, but what about my five years of research. You know, there is nothing we can do about that, and I think that is just a reality that we need to deal with, and it is a danger of moving too far up into whenever things start with Phase I in adults.

Ethical reasons are that you are again trying to optimize the potential benefit for your patients and trying to minimize the risks of toxicities.

[Slide.]

For targeted agents or biologically-based agents, we would say that you would want to start in pediatrics perhaps upon the detection of targeted biologic activity in the Phase I studies.

This has to do with some of the same pragmatic reasons in terms of limited number of patients and drugs that are going to disappear, but also one component, and we will talk about this more, is that with the new biologically-based studies, they are often asking for correlative studies that can require invasive procedures in children, so there is an additional ethical reason beyond the benefit and risk ratio, but also talking

about the regulatory limits on invasive research procedures of greater than minimal risk in children.

I think that this is a pediatric reality, that regulatory and ethical differences between adult and pediatric Phase I study conduct is an issue and a challenge to pediatric drug development.

[Slide.]

So, the last point about special challenges and innovative approaches within the development of agents for targeted therapies, the pediatric reality is that children may receive an experimental treatment posing potentially greater than minimal risk if there is the potential for direct benefit. That is what can allow us to do a Phase I study in a child and give them an experimental drug.

Children may only participate in research with no prospect of direct benefit to the child, such an invasive tissue collection that is done only for research purposes provided the risk represents a minor increase over minimal risk.

That last quotation, "provided the risk represents a minor increase over minimal risk," has

caused a lot of meetings to be had, a lot of definitions to be promulgated, and I don't think there is a clear answer on that topic quite yet, but this is a pediatric reality.

[Slide.]

Now, when you have these two components in the same Phase I study, I am going to give you a new drug, we are going to try to monitor what is happening in your tumor, the IRBs that are approving these have to consider what the whole experiment is.

The potential benefit that comes with the experimental agent, the drug that you are giving the child, doesn't give that experimental procedure that you are necessarily going to do, an invasive biopsy of liver, let's say, any benefit if there is not a clinical decision that is being made based on the biopsy results, if all you are doing is getting research information, and the family and the clinic never finds out about that, that does not necessarily flow one to the other.

So, the risk-benefit analysis is considered separately for these two research components within that same Phase I study.

[Slide.]

We think that in pediatric oncology, a major challenge then in this time of biologically-based and targeted agent development, is to develop pediatric alternatives if an invasive biopsy is what is thought to be needed during the adult studies.

Minimally invasive surrogate tissue sampling is something that should be looked into. In our studies that have been proposed and are underway, they are usually buccal mucosa, sampling peripheral blood cell studies that are done, such as in a PS341 study where they are looking at the proteosome levels in peripheral bloods cells as a way of monitoring the effect of the drug, and bone marrow cells are another relatively less invasive surrogate tissue.

Tumor cell isolation from accessible tissues, such as peripheral blood or bone marrow is another approach, the non-invasive imaging modalities that Dr. Reaman mentioned, and also the idea of correlating through PK in children, drug levels that have been associated with antitumor activity and/or target modulation in either the preclinical models that we would hopefully see in studies done from the preclinical testing program

or actually in adults during the Phase I studies that were preceding the pediatric studies.

[Slide.]

Another component or another issue that has been a challenge I think, and it just reflects all our discussions today, all the drugs that we have been talking about or all the issues we have been talking about have to do with the fact that all these drugs are designed for adult indications. That is what goes through people's minds when they come up with the drug.

[Slide.]

Maybe now in the days of biologically-based and focused drugs, that may be less the case if there are biologically-based reasons that make the adult tumor and the pediatric tumor similar, but we think that the pharmaceutical sponsors have lacked an incentive to develop pediatric-specific targeted agents, and things such as the fusion proteins for Ewing's sarcoma or for the alveolar rhabdomyosarcoma, the PAX forkhead, those types of targets are not usually listed as what people are either testing their agents against or what people are focusing their drug development efforts at.

So, we have asked in NCI whether through grant programs, is it possible to stimulate the development of agents that would be actually, from the moment they are designed, meant for pediatric development.

There is the NCI RAID program that addresses this somewhat.

[Slide.]

But we currently have a solicitation that is a Small Business initiative within the NCI, a contract proposal for the development of novel agents directed against the childhood cancer molecular targets.

This can be found on the web site. It actually closes in November. It is something that opened up in August of this year, but this is money that would be brought to a small business that had perhaps a series of agents that could be focused onto pediatric targets.

[Slide.]

Similarly, there is the FLAIR grant mechanism within NCI that would allow--it also is a Small Business initiative--but it would allow either an academic PI or a small business to bring forward their drugs, and could be used for

pediatrics, as well. The current grant closes November 12th.

[Slide.]

In summary, we see the future progress depends upon a well-functioning and maintaining that well-functioning infrastructure for early phase studies in children, the prioritization among available agents through perhaps a preclinical testing program, access to new agents from pharmaceutical sponsors, innovative adaptations of clinical research approaches to the pediatric realities, and throughout all this, maintaining public confidence that pediatric cancer drug development is being done, conducted with the best interests of children in mind.

Thank you.

DR. SANTANA: Thank you, Barry.

Could I ask Susan to give her presentation.

Children's Hospital & Specialty Group Perspective

Susan Blaney, M.D.

DR. BLANEY: I would like to thank Steven for inviting me to address you this morning. What Steven asked me to do was to provide some input into the optimal timing of the initiation of

pediatric clinical oncology studies from an institutional perspective and from a smaller consortium, such as the Pediatric Brain Tumor Consortium.

Barry has given you some background on what the Pediatric Consortium is, and its primary focus as a smaller consortium is to develop new and innovative therapies specifically for children with brain tumors.

I don't think I need to tell this audience that we have a long way to go in the progress for the treatment of children especially those children with brain stem gliomas, glioblastoma multiforme, and infants with brain tumors.

A lot of this you have heard already, so I will try to be brief. I think we all have a lot of consensus on a lot of the issues that we need to address, but is a historical timing for the initiation of pediatric Phase I clinical trials.

Historically, this has occurred following the assessment of initial safety data and reasonable evidence of potential benefit, so what does that translate into? As Peter told you earlier, for the most part, it is after the completion and publication of adult Phase I and

usually Phase II clinical trials in adults, so that means when the Phase III studies are ongoing or nearing completion.

[Slide.]

However, in some cases, it is following the completion of adult Phase III clinical trials, and the worst case scenario is following the successful New Drug Application by the pharmaceutical company, but I have been involved in studies where the trials are initiated in children at the first signs of biologic activity in adults, and there are instances where the submission for the IND application included both the pediatric and adult Phase I studies.

There are also other instances where pediatric Phase I studies are initiated in the pediatric population exclusively, for example, monoclonal antibodies that are specifically targeted to receptors on the tumor cells or cytotoxics for intrathecal administration.

[Slide.]

This has already been shown to you in several ways this morning, but just a different way of looking at it, is this bar graph where, on the y axis I show you the time in months, and then down

on the x axis is a series of drugs.

What this represents is the timing at the initiation of accrual to Phase I pediatric trials after publication of the adult Phase I results.

Now, I have been very generous to our adult colleagues in this top, giving them a 12-month period for completion and publication of their results. I think that is overly optimistic. I think it is really closer to 24 months, in some cases even longer.

If you just take this area that is more lightly shaded down here--it doesn't project very well--the average time is at least two years after publication of the adult Phase I trials, so that means when we have evidence of efficacy, usually in the Phase II setting, and as was mentioned before, when the Phase III trials are ongoing.

But there is a lot of heterogeneity and with some of the newer agents, we are getting earlier access.

[Slide.]

This is just an example of one agent where a worst case scenario with the Phase I trial, the drug was initially developed overseas, and the Phase I trial results were published in 1991. The

adult Phase I trials were published in '93. The drug was approved for adults in 1996, and it wasn't until '96 that the Phase I pediatric trials were initiated.

[Slide.]

Now, just to put this into perspective of what this means for children and the overall impact on pediatric drug development, that here we have the approval, here we have the initiation of the Phase I trial, which generally takes a period of two years to complete.

The Phase II studies, which on average for broad-based Phase II studies of the cytotoxic agent take three to five years to complete, it doesn't mean that for some strata there is not earlier evidence of activity, but the overall study.

Then, assuming that the agent goes to Phase III to see if it makes an impact, there is five years at a minimum until the completion of the trial and perhaps even longer until we know the improvement and progression for survival or long-term survival.

So, this is overall from the time just taking preclinical into consideration for adults, and as we talked about before, sometimes we don't

have that preclinical data until later in pediatrics, almost 20 years, and that is a long time, and that is why it is critical for us to get earlier access to drugs, so we can shorten this timeline.

[Slide.]

Here is just another example of a drug that we did have earlier access to, and even still from the time the Phase I study was initiated until the time the Phase III trials will be completed, it is almost a 12-year period, so that is why early access is critical.

[Slide.]

So, what is the optimal timing for the initiation of pediatric clinical trials? I think that it is obvious there is not going to be one single answer, that we are going to have to look at these drugs on an individual basis, but here are some considerations that I think are important in looking at.

The first is the type of agent and its mechanism of action. Is it a novel agent or is it an analogue, had aphasia for analogues. Some things aren't necessarily analogues, but they affect the same target.

Is it a nonspecific cytotoxic agent or broad-based agent versus an agent that has a specific target, and I think we are naive to think that we have those agents yet, but as we become more sophisticated and know more about the biology of our tumors.

What is the underlying disease being treated? Obviously, it is going to be very different if we are treating a patient for whom we have no effective therapy, no curative therapy versus relapse patients where we have a good chance of salvaging them with currently available agents, so I think that is a very important consideration, as well.

[Slide.]

In addition, what is the safety profile of the agent. I am taking this from the perspective that we have an ideal world and we know from our preclinical studies that we have an agent that looks very promising in pediatrics, so what is the safety profile of the agent from initial adult clinical trials, or is it specifically an agent that is targeted for pediatrics and the preclinical model systems that we use.

Then, for agents, this has been alluded to

this morning, the availability of pediatric formulations.

[Slide.]

The primary focus of considering when we should initiate pediatric trials I think should be for those novel agents and agents with novel mechanism of action, so what are the considerations and the timing for initiation of drugs with novel mechanisms of action.

I think early initiation is critical, and that is a common theme this morning. We need to develop strategies and new agents to improve the outcome for children with incurable brain tumors or other high-risk pediatric tumors.

As Peter talked about in his earlier slide, one example with cardiotoxicity from doxorubicin, however, in children with zenith tumors, in those children that do survive, many of them have severe morbidity or long-term neuropsychologic or neuroendocrine sequelae as a result of the need for radiation therapy. So we need to try to identify agents or treatment strategies that can minimize the toxicity for these patients.

[Slide.]

So, what is early initiation, how can we define that? I think there should be evidence of biologic activity in adult Phase I trials, and how do we define biologic activity, that is going to depend on whether the agent is a cytotoxic or whether it is an agent that we expect to have an impact on a target or a surrogate target that we are monitoring.

I think we should initiate these trials upon determination of the MTD and/or optimal biologic dose, and sometimes even earlier depending on what the agent is and what our preclinical activity is.

If the target is primarily pediatric, I think it goes without saying that upon the completion of adequate preclinical studies, and those could include both in vitro and in vivo studies.

[Slide.]

When should we initiate trials for new analogues, and this is a point that has already been raised this morning. I think there is a number of issues we need to consider - does the agent have equivalent or superior activity in preclinical studies, are there any advantages to

the toxicity profile, are there advantages with regard to potential for drug interactions or lack thereof.

Another advantage is with regard to the formulation for the pediatric population, but lastly, there should be evidence of at least equivalent or, if not, superior activity in the adult situation for development of analogues. Our focus should be primarily on developing new agents with novel mechanisms of action.

[Slide.]

In conclusion, I think that we are not going to have one uniform recommendation, that the timing of initiation of clinical trials historically has been highly variable and in many instances has not been optimal, that ongoing communication between the pediatric cooperative groups, industry, the FDA, the NCI, and our patient advocates is required to ensure the earliest possible access to promising new agents with novel mechanisms of action.

[Slide.]

Pediatric studies for novel agents should be initiated as soon as there is evidence of biologic activity and an acceptable safety profile

in early Phase I adult clinical trials, and that early access requires ongoing vigilance and constant reevaluation to ensure optimal prioritization and potential for benefit for children with recurrent or refractory cancers.

It is not a static process. It is going to continue to be an ongoing and dynamic process.

DR. SANTANA: Thank you, Susan.

We have a few minutes to entertain comments or questions to these three presenters, if anybody has any comments.

Peter.

DR. ADAMSON: I had a comment that stemmed from Barry's presentation, that I think is worth hearing perhaps from some other people. I think part of it has to do with perceptions and misperceptions with regard to the conduct of Phase I trials in children, as well as the ethical considerations.

To start with, I think one misperception that industry has is that an obscure toxicity in a child could derail a drug approval process, and I think Dr. Pazdur at another meeting clearly came out and said that he knows of no example, and I certainly don't, of where a drug was not approved

because of an obscure toxicity in a child. Drugs don't get approved in adults because they are not effective, and not because of toxicity.

So, the fear that there is going to be a toxicity that will derail development is a perception that we need to correct and to overcome.

The other point was that I think the ethical considerations for the conduct of Phase I studies in children are likely much more closer to that in adults than is recognized by our adult colleagues.

Yes, children are afforded special protections, but when it comes to correlative studies, I think over time it will emerge that the ethical considerations we apply in children, in fact, ought to be applied to adults.

I know this is not a topic for us because we are focusing on pediatrics, but requiring studies that are invasive and of no potential benefit, we will not do that in children, however, I think the requirement to do that in adult patients with refractory cancer is coercive, and the requirements about a study not being coercive are the same between pediatric studies and adult studies.

Skip Nelson may want to comment on that, but I think the idea that you can require all these studies and therefore we can easily do these studies in adults is a misplaced one. Over time, when it is recognized that these invasive procedures that are of no direct benefit and the only way an adult patient can receive an investigational drug is to agree to that, is coercive.

So, I think we are going to face the same set of challenges in adult Phase I trials as we face in pediatric Phase I trials, when the community arrives at that, I can't say, and if pediatrics leads the way in the discussion, it won't be the first time in oncology that pediatrics has led something.

I don't know if others want to comment, but Skip, who is really much more eloquent at discussing ethical issues, may want to add to that.

DR. SANTANA: Skip.

DR. NELSON: I really don't have much to add, Peter. You just demonstrated why you are a valued member of one of our IRB committees.

DR. PAZDUR: Let me follow up on that, though. I think in adult oncology also, that would

be looked at as coercive, and there is very few IRBs that I know that would let that go by.

Usually, the correlative study, when it does involve a biopsy, if it is labeled as an optional procedure, it generally requires a separate consent form, and if it is an integral part of determining whether the therapy goes on or assessment, then, it could be bought into as a required procedure, but that has to be, as was mentioned in the NCI presentation, an integral part of a decisionmaking process.

So, a very similar philosophy that was presented for pediatrics also holds for adults, too.

DR. ADAMSON: I don't think the NCI shares that philosophy.

DR. PAZDUR: Do you not?

DR. SAUSVILLE: I just would state that this is a fairly controversial area, and I also think it is colored by one's perceptions of degree of invasiveness and also, quite frankly, how the physician pitches it to the patient.

I definitely agree with Rick that in any context to require it would be regarded as coercive, so there is clearly, you know, we buy

into that.

However, it is also true that we sometimes place trials--and Malcolm or Barry may want to comment on this--with patients that are likely to have accessible tumor because of the likelihood that the average adult would not consider it much of a big deal, for example, to get a skin biopsy.

I could come back to you and say that if you even put it in the context of a relatively non-invasive treatment, and how would you shape a pediatric approach to this issue where at some level, a buy-in on the part of the patient is required, so I think it is complex.

We share your goal of minimizing and indeed eliminating any perception or practice of coercion, but nonetheless, even in a minimally velvet glove scenario, one can imagine that adults are going to be intrinsically better able to enter into a decisionmaking process in children.

DR. KODISH: I wanted to engage Barry in a little ethical discourse here, because I heard an interesting mismatch between what I perceived as Barry drawing a line in the sand about the appropriate timing for the cytotoxics that is based on completion of the adult Phase I, ready to go to

Phase II, and it was different than what I heard Susan say, which is that we need to have more flexibility, that there may be some instances where it would be okay to do simultaneous studies or to start the pediatric Phase I study halfway through the adult study.

I think that you are right on the money when it comes to the targeted agent issue and this idea of separating out the components of the research as you mentioned, but I think we need to work a little bit on this cytotoxic approach.

The ethical argument I hear underlying your comments is that the imperative of avoiding toxicity in children is greater than the imperative of avoiding toxicity in adults, and I am not sure that is true necessarily.

I think it gets to this issue of how vulnerable are children, are they biologically or physiologically vulnerable in some way or are they ethically vulnerable. The regs deal with the fact that they are perhaps ethically vulnerable, but in these studies, there is potential for direct benefit.

So, to me that was a concern.

DR. ANDERSON: I think that if you were to

say we should start simultaneously, it would be a question of is there a benefit that has been demonstrated along the way. If you are not going to derive what I see for pediatrics, the benefit of defining the toxicities and starting the patients out closer to a potentially active dose, if there ever is one, then, it would be a question of what activity was seen early on as the adults were going up through their dose levels perhaps, towards an MTD, because that was the endpoint that they were ultimately focusing on that would bring you to do that in pediatrics.

I don't know, you know, other people have other opinions about starting them simultaneously, and I would want to know what the benefit of doing that would be. If you had truly, you know, if Peter was saying, well, we now have 45 drugs that we are trying to do studies on, if it is a matter of we want to get access to this drug at the same time, but we don't know if it is active, I don't know if there is a benefit to that.

DR. BLANEY: Two things. One, I think that we don't need to evidence of benefit in the adult Phase I study before we initiate a pediatric trial. We have to have potential for benefit, and

usually that is based on our preclinical model systems in childhood tumors.

Now, in most case scenarios, I would not argue that we should have simultaneous initiation in the trials, but we could have simultaneous submission of the protocols with the IND and have a predefined goal for what is going to allow us to initiate the pediatric study, is that biologic activity as evidence of myelosuppression for a cytotoxic, is that an effect on the target tumor in a range that we think based on preclinical pharmacokinetics and the pharmacokinetics from the adult Phase I study where we think there would be potential for benefit in our population.

DR. SANTANA: I agree, Susan, but I heard a comment this morning from our friends from industry that we don't want to get into the trap, if they are not getting a hint that this drug is going to have activity in adults, they may drop it, and we would be faced with the same problems we have in the past, but there may be some drugs that we do want to develop, but if we can't get them to demonstrate at least some activity even in the Phase I, then, we may be losing our time and our patience and our resources.

So, I think we have got to be careful. In the ideal world, I think you are absolutely right. In a very practical way, I heard them say this morning that to them, it is an important consideration to begin to get some evidence of activity, because if not, they are not going to develop it any further, and then nobody has access to it.

One last comment?

DR. HAGEY: I think now might be a good time to comment on attrition rates of drugs. The TUFF study for drug development looked at 671 new chemical entities which applied for an IND between the years of 1981 and 1992, and of those, only about 135 were actually approved, which is around 20 percent.

If you take that and break it down by oncology drugs, I think 33 with a final approval of 6, and 6 still waiting, I know that is the data as of 2000.

About 26 to 30 percent of the attrition rates occur in Phase I with over 50 percent of the attrition occurring in Phase II, which would argue, in fact, for the current model, which seems to be most of the time pediatric studies are initiated in

Phase III, which looks like about that time you have about a 75, 78 percent chance that indeed that drug will go to market.

DR. SANTANA: I think with that, we are going to stop here for a lunch break.

[Whereupon, at 12:30 p.m., the proceedings were recessed, to be resumed at 1:10 p.m.]

AFTERNOON PROCEEDINGS

[1:10 p.m.]

DR. SANTANA: There were two individuals that were not present when we did the early introductions this morning, Dr. Emanuel and Dr. Kodish, so I am just going to ask them very briefly to identify themselves and their affiliations.

DR. EMANUEL: I am David Emanuel, clinical oncologist out of Pharmacia Corporation.

DR. KODISH: I am Eric Kodish, the Director of the Rainbow Center for Pediatric Ethics in Cleveland, Ohio.

Open Public Hearing

DR. SANTANA: The first item on the agenda for this afternoon, just to keep this item on schedule, is that we have an opportunity for an open public hearing, so if there is anybody in the audience that wishes to address the committee, please come forward at this moment and identify yourself at the podium.

Please identify yourself and you may proceed.

DR. RUGG: Good afternoon. Thank you. My name is Terry Rugg. I am currently at Immunomedics, Inc.

I have just three comments I thought I would make. The first one is very specifically to I guess the regulatory aspects of getting studies done in children. I have had experience in prior companies where drugs have, from a regulatory perspective, been able to get in very quickly, and more recently, a highly targeted therapy in AFP-producing tumors, which you might argue is very different from hepatoblastoma and adult tumors, where there is a very definite view on the biological division of the FDA that closed the door very early.

So, I think if this forum does focus in on the regulative facilitation, which I think is what the question is all about, I think that would be very important. That is one experience.

The other two comments really I make now in reaction to some of the thoughts and some of the things that I have heard earlier this morning.

Firstly, just a quick thought, the issues regarding getting material transferred to institutions for applying in the preclinical setting. In the spirit of very clear communication, I think it is important to say when you negotiate these things, never ask for that

which the other party cannot give.

The other party cannot give intellectual property away. From my experience, a number of times these agreements have fallen apart because the receiving institution has legal requirements, require intellectual property to be seeded by the pharmaceutical company, it is never going to happen. My colleagues I am sure will agree it is never going to happen.

The final thing that I will comment on, which has been referred to a number of times, but always very subtly, very under the surface, and very not obviously, and that is the reality that a drug that will have only a pediatric indication cannot be commercialized, and when I look at all the participants here, every one of us are M.D.'s, every one of us has research interests, I don't see anyone with an MBA or I don't see any of my marketing colleagues, I don't see anyone who would represent the finances, which means that a lot of what we talk about here cannot ultimately influence the practice. The practice has to be influenced at a political level that results in drugs being reimbursed in some way of another or a system that meets those needs.

I think, David, you recognized that to an extent, but it is a barrier bigger than you would think. My nightmare would be having a drug that worked in the pediatric setting, but did not work in an adult setting, because I wouldn't really know what to do with it. I couldn't market it and I couldn't withdraw it, and I would be bankrupt.

So, with those three observations, I leave the podium and I thank you for your opportunity.

DR. SANTANA: Thank you. I am sure we will come back to your comments during the open discussion.

I will ask David Emanuel to give his presentation.

Industry Perspective

David Emanuel, M.D.

DR. EMANUEL: Thank you, Victor, and thank you, Steven, for the invitation. I greatly appreciate it.

What I have decided to do is to gut my talk and to actually focus just on some issues that we haven't addressed up to date.

Just before I start, I just wanted to make the point that we all agree that the status quo is unacceptable. Every person in the room, I think is

on the same page with that. We all agree that we really have to move on. The question is how to get there.

So, what I wanted to do is really not to talk about the barriers, because really the barriers that I saw are exactly the same as everybody else has seen. Let me just run through and go back to my final slide, in fact, I have only got one slide to show you, which is overcoming these issues.

[Slide.]

At the workshop that was held at the FDA in July of 2002, the issue was raised about lowering the regulatory hurdle as a means for encouraging development of drugs in the pediatric setting.

I think this is an issue that the committee should really look at because I have heard a couple of times today that registration in a pediatric indication is quite important sometimes, not all the time, but it is important from the point of view of the reimbursement, et cetera, et cetera, and I think you raised this issue this morning in Europe.

But from the pharmaceutical companies'

standpoint, from the dark side, registration is what we are all about, and I think it really does bear some thinking about when we discuss things like is it really necessary to do an adequately powered trial, I mean it is literally impossible to do this in the context of the pediatric setting. It would take years and years and years.

So, I know this is a heretical statement, but how important is the randomized trial. That is the first question.

The other two things relating to some of the regulatory issues are the definition of clinical, what does this term actually mean in the context of a child, clinical benefits. Clinical benefit is what we are all trying to achieve with our drugs, but in pediatrics, I would very much welcome input from the committee and from the FDA about what does this actually mean in a child with a malignancy.

One possibility would be for us to prospectively define acceptable surrogate endpoints which could take place, which could be used in place of, quote, unquote "clinical benefits." I am not sure what these are. It is not up to me to really define that, but I think input from the

committee, input from the field would be extremely helpful. Clinical benefit is key here.

The second point on here, increased access to the patients. I think the tables have turned. We have heard this many times today. There are too many drugs to get into too few, quote, unquote "eligible patients," and this is a major problem, it is a major barrier, and it is one that we have to work on together and to support Greg on this.

Communication is the absolute key. We are not talking to each other. We really need to increase the intensity and the depth and breadth of the communications across all these groups.

I am talking about the COG, industry, NCI, FDA, all the cooperative groups outside the United States. We really need to communicate better because, quite frankly, it is not working, and I think the key to success is improving, is just getting us to really understand each other and to really talk to each other.

Some of the benefits that might accrue from that - the issue about ex-U.S., how can we increase enrollment into trials outside the United States. There are lots of kids with the kinds of diseases that we are interested in, in Russia, in

Eastern Europe, in Africa.

The FDA has told us that they accept these places as sites for trials. How do we have access to those? I am proposing that we do joint transnational clinical trials, sponsored by both industry, by the NCI. We have to get access to the patients. That is absolutely key.

Prioritization of scarce patient resources is exactly the same thing.

Expedite initiation and execution of trials. From the industrial standpoint, this is a major problem. It takes forever to get these things done through the cooperative groups. I am being very frank here, but this is why we are here, to table issues.

Industry lives and dies by the timeline, and the timelines that we work under are completely different to yours. We have to get ourselves aligned on that issue. We have to improve this.

Jointly funded development of drugs. This is a whole issue unto itself, and we have just touched on the issue of MTAs and CRADAs and intellectual property.

We were just talking at lunch. I want to again stress the point that was just actually made.

Intellectual property to the pharmaceutical industry is its bread and butter. We will not give up on that. Intellectual property is a big deal for us.

When somebody brought up the issues of how long it was taking for an MTA to get signed, I will guarantee you that that took that long because of an intellectual property issue. We have to work out ways to get around that, otherwise, it is just going to continue to take as long. Intellectual property is a big deal to us. This is something that we will absolutely refuse to budge on.

Excuse me for jumping around. As I said, I gutted my talk.

I guess the last point that I wanted to make, which has been raised by others, is we all agree that from the pharmaceutical company perspective, whether the Pediatric Rule, the exclusivity terms, et cetera, have worked, it is too early to tell, but I can tell you where it has worked.

It has worked in internal discussions with our senior management. Any one of us who actually works in the industry will tell you that getting money from the people that control the funds is one

of our biggest tasks. It doesn't matter what we want to do, it is what the corporation would like to do, and it is a challenge for all of us who happen to work in this type of environment now to actually convince our upper managers of this fact.

The Pediatric Rule has worked from that regard. So, I make a very strong plea that the maintenance and expansion of, quote, unquote, "incentive programs," is key to the success here. We absolutely have to continue these in some form or another.

I also submit that pediatric oncology, in terms of the current ongoing pediatric drug development debate that is ongoing in the Senate, I guess today or tomorrow, I submit that pediatric oncology drug development is very unique and very different to other parts of that discussion.

I am just sort of challenging us all to think about ways that we can think up incentives to develop pediatric drugs for use in oncology.

I think that's it. Thank you very much.

DR. SANTANA: We will come back during the comment discussion period, hopefully, to some of the issues that you have presented.

Dr. Rackoff, are there on the phone?

DR. RACKOFF: Yes. Victor, can you hear me?

DR. SANTANA: Yes. People want to know where you are. Are you going to make some comments now, Wayne?

DR. RACKOFF: Yes, from Bersa [ph] Belgium.

Industry Perspective

Wayne Rackoff, M.D.

DR. RACKOFF: I have really only three comments, and I want to drop off soon.

The first is that much of what has been said today has been said in the other three or four meetings we have had, and I think we have got enough information now to have the agency move forward with some sort of guidance on these issues.

I think that two issues that are particularly pertinent that were touched on today have to do with preclinical testing, and I think what would be very helpful is if those that are involved in that consider not only the pediatric models, but also what correlations there are between their pediatric models and adult tumors, and actively work on identifying those correlations because they will provide further help to us in

pushing these drugs toward children.

The third and last point is that I think that there probably needs to be some sort of priority setting between the Children's Oncology Group and the Agency as part of this process, because I think it is much different to do studies and also much different to introduce a drug earlier in an area of more severe need like Stage IV neuroblastoma than it would be in ALL.

I guess, as a last point, a sort of summary, I take a little bit of issue with some of the comments that have been made so far and agree more with I guess Greg Reaman and some of the others who have said I think we have made tremendous progress.

I think that those who are not part of the dialogue either at these meetings or at the COG should become part of that, and I think the impetus is on individuals on all sides to participate and help this process move forward.

DR. SANTANA: Just for the sake of completeness, is that it?

DR. RACKOFF: Yes.

DR. SANTANA: Thanks, Wayne.

We are going to invite Ruth Hoffman to

give the patient and parent perspective.

Patient and Family Perspective

Ruth Hoffman

MS. HOFFMAN: I wanted to also thank Steven for the opportunity to speak from the parent-patient perspective, and I think it is a very important voice.

[Slide.]

First of all, this it not derived from a formal survey like the ASPH/O survey that was discussed earlier. It is basically a shared perspective from my position as a parent of a child, a 15-year survivor of AML, who actually is dealing with cardiotoxicity from 400 mg/M 2 of anthracyclines, as well as hormone replacement therapy, as well as interaction with thousands of families through Candlelighters.

[Slide.]

So, who is the constituency? Thirty-two years of supporting families of children with cancer, and they are very active as you can see. We receive about 6,000 phone calls a year, 14,000 e-mails, and 155,000 web site visitors. That is about 14,000 unique visitors per month, which equates to 1.5 million hits, huge.

What is it that they are asking? Approximately half the queries are connected to treatment-based questions like what are available clinical trials, what is a clinical trial, as well as institutional referrals, where is the best place to go with my kid who was just diagnosed with neuroblastoma, what are the best surgeons, where are they located. That is the sort of questions that we got. The rest are financial assistance, and that sort of thing.

[Slide.]

So, because of that, in the last month we actually--I don't know if you know this web site or this service--we just started HopeLink, which is a clinical trial service to our web site, which basically incorporates clinical trials from industry, from institutions, as well as from COG. At this point, there is 385 trials just children-based and they are Phase I to Phase III.

[Slide.]

What is it families want? They want hope. This was an example when I was putting this together, this came through that day. "When the doctor explained to us about Melissa's leukemia, he said that APML is incurable and it's very rare and

very deadly. Can you give us hope?"

[Slide.]

What do they want? They want a magic bullet to treat their child with a resistant disease. This didn't come through. It did have a picture there of a little girl.

[Slide.]

This is the historical perspective. Grace Monaco was the founder of Candlelighters in 1970.

"The childhood cancer population is a small community in number, but large in spirit and used to success. The clinical trial process is what has brought pediatric oncology the cures that give hope and help to parents and survivors, and has created a foundation of trust upon which to build improved and novel treatments."

[Slide.]

So, the foundation of trust was based on, and must continue to be based on: Relative safety through the use of preclinical models, as we talked about, animal testing, and traditionally adult testing; the possible magic bullet versus the actual small percentage rate on the response to Phase I trials, and families want to know that information; and then, as well, the side effects of

treatment, the toxicity and the effect on quality of life at the end of life.

[Slide.]

Families--I think all my pictures aren't in here, which is actually too bad--there was a picture of a child actually on his death bed. He was shown actually with large fungal infections on a Phase I trial, and the feedback from the families--there was actually six pictures of kids--and four of those children were on Phase I trials, and in discussing with them to prepare for this, none of them had realized what a small response rate the children were likely to get on that Phase I trial, and they were very surprised and somewhat disappointed, and really felt that the doctors had not been fair in disclosing that information.

So, a need for greater information, that is the feedback we are hearing. And the option that discontinuing treatment isn't a valid option, families want to know that it doesn't mean you are a bad parent, it doesn't mean that you are giving up, and the child is not required to go down fighting, especially when you are talking about a two-year-old, and not making that choice for

themselves.

It is different if you are talking about an 18-year-old, who maybe wants to go down fighting, but for a parent making sometimes that decision for a two-year-old and continuing treatment when it can result in quality of life differences, then, that is something to be taken into consideration.

[Slide.]

A comment from Grace again. "To keep the pediatric patient lot improving, the cures growing and the effects of therapy on quality of life, particularly in the hard to handle cancers, we need to innovate within the careful, patient-centered model that pediatricians have always utilized."

[Slide.]

Industry. These are the barriers we have talked about all day - unenthusiastic, the rare pediatric tumors, small population size. A couple things that haven't been addressed, problematic access to clinical trial information, health insurance and billing concerns. For families, often their choice is either/or. Their child can receive palliative care or they can continue on Phase I curative therapy.

Actually, again, one of the pictures of the kids that was featured here went through that situation over and over. She was a neuroblastoma Stage IV child. She was on palliative hospice care. Then, she would go off palliative hospice care because insurance wouldn't cover it. She would go on a Phase I trial. Then, she would go off the Phase I trial. She would go back into hospice, back onto Phase I.

It was very, very frustrating for her family because it was not both options offered to this child, it was an either/or situation. That is a policy that really needs to be address and a major barrier.

Centralized trial information. We talk about all these drugs, not enough patients. Patients are very active, as I showed you at the beginning. They are very participatory and if we have a comprehensive web information or resource where families can go to, like HopeLink, it's not completely comprehensive, but basically incorporates COG trials, industry trials, institutional trials, again, that is information that families can use to make decisions.

[Slide.]

In terms of the innovations regarding small populations we talked about this morning, with molecular targeting of drugs and finding similar pathways, that barrier might be decreased, the correlation between genome anatomies between adults through expression profiles and somatic mutations might decrease some of that adult-child issue.

I think that we have to ensure that existing programs, such as--and maybe Malcolm can address this--the Cancer Genome Anatomy Program, NIH program, that includes pediatric tumor initiatives.

[Slide.]

This is where it becomes controversial even with parents. This is from Grace's perspective. "There is no reason that the pediatric oncology community should wait for results from any adult trial before designing their own Phase I's and pilots for the use of new and old agents in pediatric oncology."

[Slide.]

Now, we have varying degrees on this. Some parents feel that definitely we have to have adult studies done first for reasons of dose

initiation, reducing overdosing, underdosing of the kids, and safety testing.

This is a broad generalization, but it tends to lie this way. People that have lost or parents that have lost their child tend to feel there is no reason to wait. People whose children have survived, like my daughter, who are dealing with late effects, think no, the toxicities are very difficult, there is reasons to wait.

Now, that is a broad generalization, but that tends to be how things tend to fall.

[Slide.]

In terms of the small pediatric population, and these of adults, maybe there needs to be more formalized, it gets expanded formalized coordination of U.S. adult cooperative group/clinical trial studies, and then COG/academic/pharmacy child studies for simultaneous access.

The possibility of joint yearly symposiums on Phase I trials between the adults and between the children, and where you can just be discussing emergent targeted pathways that are shared by tumors, and possibly the design of consortiums based on molecular pathways, not based on tissue

and cancer, so not the Brain Tumor Consortium, not necessarily the NAT Consortium, although those are wonderful consortiums, but possibly consortiums based on molecular pathways.

[Slide.]

If children are going to benefit from adults trials, we have some need to expand on that, and being a Canadian, I have to bop this one in, in Canada, most of you probably don't know, but we have between a 60 and 70 percent clinical trial rate of adults in Canada on cancer clinical trials, it is about 5 percent here.

I don't know if they have an increased survival, as well, but it is a huge clinical trial participation of adults and about 90 percent of adults are treated in comprehensive cancer centers. Now, there is your market if you need to expand and need more adults, that is maybe a potential market.

[Slide.]

Another market that has been talked about is internationally. This was another e-mail that I received the same day I was putting this together.

"I am writing on behalf on my friend's sick child. Could you please send me some information on international treatment resources

available for a child who has leukemia, acute lymphocytic form. This is a boy and he lives in Ukraine. Resources are limited there, but I heard that in Russia some clinics successfully treat this disease. If you need more information about him, please let me know" - blah-blah-blah.

[Slide.]

So, again, increase the collaborative Phase I international trials. Increase the collaborative international preclinical trials.

[Slide.]

Finally, the point about communication. Utilization of a common, comprehensive child-specific clinical trial information service that is used by academia, by COG, by NIH, by industry, and by individual institutions.

[Slide.]

This actually was set up with several children. All of them have died. The one in the bottom lefthand corner was a little girl with osteosarcoma. She was 10. She actually used her legal right of assent and countered her mother. Her mother wanted her to go on trials, and she had already been on treatment for three years, and she refused. We were brought into the case at that

point, and she actually spent the last four months of her life having a wonderful quality of life, went to Florida, went to California, and actually had a very peaceful death.

A couple of the others who actually went on a Phase I trial had a very difficult death, and the one mother said to me that she has a double grief, you know, the grief of losing her child, but also the grief of putting that child through extra pain.

Now, she also said she would do it again, and she felt that she had no choice, which gets into again other issues, but I guess the big point is, is I think we need to have a balance in what we do, and sometimes I think we need to keep this in mind as a guiding principle that life isn't measured by the number of breaths we take, but by the moments that take our breath away.

DR. SANTANA: Thank you, Ruth.

We had a couple presentations earlier today that we didn't have the opportunity to discuss and ask questions to the presenters. I know some members of the panel do want to do that, so this is an opportunity to start that.

Donna.

Committee Discussion

DR. PRZEPIORKA: Two questions. First, for Dr. Adamson. A point just brought up by Ms. Hoffman regarding cooperation between adult and pediatric groups, we had once actually talked about that at a previous meeting, and I just wanted to know if any headway had been made in that direction, and if talks have begun, have you come up with any impediments from the adult side saying no, we don't want to deal with kids in our protocols.

DR. ADAMSON: I think I can answer, but I am going to need some clarification on that. With the new Phase I consortium, we just had our first meeting, and we are going to be meeting semi-annually.

The meeting was held in conjunction with the NCI CTEP-sponsored adult Phase I group, and we plan to continue that, so all the pediatric representatives were there to hear about what is happening on the adult side, and as importantly, we made our presence known to NCI CTEP that hold these meetings that didn't regularly include pediatric representation.

So, I think from that standpoint, we have

improved communication and, in general, we have a good sense of where the adults stand in reference to their trials, and this is I think just adding another layer to make certain that we are aware really of the most recent advances.

Can you clarify your last point for me? Oh, that was it? Okay.

DR. PRZEPIORKA: I think you should be lauded for getting that far in this short a period of time, to be sure.

My other question is actually back to the FDA. I don't think I was clear when I was making my question earlier today.

The usual paradigm in drug development and drug registration is for a pharmaceutical company to come by, do their studies with the idea of getting registration and selling their drug, and we are here talking today about where we can get the pediatric studies to get going either for registration for a pediatric indication or just to get some information for pediatrics.

But what we have heard is that we don't need adult studies first, we could do this in pediatrics except we just heard that it is not really economically feasible to do that. There is

one other paradigm that we need to talk about, which addresses directly the regulatory burden that Dr. Emanuel talked about, as well.

As an example, there is an institution in the East which makes its own biologic and uses it to treat leukemia patients and has been doing so for about 12 years. They charge the patients, and they live happily ever after, and if you ask them for some, they say no, we only have it at our institution.

They do that so that they actually get the market share of those patients with that disease, which will then feed their other protocols and bring in more grants. That is the only economic incentive that academics have to make their own drugs and to deal with the economics of doing clinical research.

But for an academic institution to start any study of a drug in a pediatric population or any orphan disease, there has to be some sort of endpoints to the money that they invest, and they don't have anywhere near as much money as pharmaceutical companies do, and especially if it's an orphan disease.

So, there is only an incentive to go and

study pediatric drugs if at some point they can stop and start charging for the drugs they manufacture and stop having to deal with the paperwork burden of reporting.

If an academician comes to you at the end of their Phase II study, and a disease which has absolutely no good therapy, and they say, look, our drug has a 30 percent response rate, can you just give us approval to deal with it, so that we could like start collecting money for it, and not have to tell you anything about adverse side effects, and we don't have enough patients in the world to do a randomized trial, what would you say?

DR. HIRSCHFELD: Go for it. There is an orphan program that has been in existence for almost 30 years, and that program has successfully brought well over 100 drugs to be approved for marketing in a variety of diseases, many of which are rarer than pediatric oncology.

To give some perspective, the number one medical reason that causes children to die are tumors, overall, it's access, but of all the diseases that affect children, the number one cause of death is tumors, and I think that can be used as a justification for entering into a program, but

that is a whole other discussion in terms of the marketing strategies, and whatnot, which are certainly beyond the realm of not only what we are discussing today, but probably what I should be talking about.

But I can address the idea of the orphan drug program, which offers people grants, it offers incentives, and there are dozens of cases of people who essentially in a single institution, develop, oh, an inhibitor of an enzyme that is over-expressed in some rare genetic disorder and then have successfully gone on to market that.

There is no reason why it couldn't be applied more widely although the resources are limited in pediatric oncology, however, I will point out that we looked at how many people actually filed and asked a question we have a product, and here is our data, and can you give us marketing authorization for a pediatric tumor, and the last one we had was in 1990, and that was for a drug called teneposide.

Since then, no one has filed a single application or a single supplement to an application. So, if it would come across our path, then, we could address and ask for it, but we can

only indicate interest, we can't compel.

We can provide incentives, however, and the incentive program I think has been reasonably successful and that we have had roughly 30 invitations out. About 15 are for investigational drugs, and we have actually granted 2 of them to date, and there are several others. On reviewing, this had never happened before in the history of the regulatory aspect.

Now, I wanted to introduce a term, since we brought it up, and the term I will try to introduce is the term "orphan drug." The Office of Orphan Drugs is actually for orphan indications or orphan diseases, and they call it that, but I wanted to propose that the circumstance where a drug is born, and it is developed up through Phase I or early Phase II, and then abandoned by its parents, that that is the orphan drug.

One approach to think about that orphan drug would be to go back to the ICH guidelines, which say that it is the shared responsibility of society to address these issues, and there could be, and maybe ought to be, programs to pick up these orphan drugs and develop them in niches where they may have activity or may have some benefit.

I know Rick wanted to make a few comments, too.

DR. SANTANA: Go ahead, Rick.

DR. PAZDUR: There are several questions to answer there, Donna, and let me go through them.

Number one, for somebody that is coming in with a hot drug on Phase II data, that has a 30 percent response rate in a disease situation where there is no other therapy, it is clear that that would be a situation for accelerated approval, and that would be a very, very hot drug. You do not know the numbers of companies that are coming to us seeking accelerated approval on that type of data, what is a niche indication that we could have.

Remember, we are being asked to develop drugs or people are coming in to develop drugs with increasingly more refractory disease settings, fourth line lung cancer, fifth line breast cancer, fourth line colorectal cancer. That isn't because they have an interest in that population. Obviously, their business decisions are geared toward a much bigger population and they could get their foot in the door in these niche populations.

So, the fact that pediatrics has a small market here should not be overlooked. That is a

way that companies could get accelerated approval.

But I want to go into a very important aspect that was made by Dr. Emanuel, and that was the slide that says "lowering the barriers." Dr. Emanuel, I call that lowering the standards, okay, and I don't know if that is what you, as pediatric oncologists, want to get into as far as having your drugs approved on different standards, i.e., potentially less effective drugs being approved.

Let me go into some graphic detail. Do you want to throw out the baby with the bath water here? You have made tremendous strides as far as curing the diseases. The things that were listed on the slide, using less power or toning down the power of your studies, that really leads to faulty statistical decisions.

That is not a regulatory issue to accept less powered studies or shaky studies just so you could get a drug on the market. Do you want to be in that predicament?

That is a situation that you have to answer yourself. The situation of clinical benefit, we have defined that quite clearly in the adult population, and I don't see any designation of any difference with children. Basically, it is

what is meaningful to the patient, and that generally has been assumed to be an increase in survival and increase in symptoms, or a surrogate that is well established for those two issues.

Do you want to get into again lesser standards just to get drugs out on the market? That is a question again that you are going to have to answer.

To get back to Donna's issue about the poor university person coming to the FDA, we do not have different standards for small drug companies versus big drug companies. It is an even playing field, okay, because that small drug company with a flick of the Bic could turn into a major pharmaceutical company with an infusion of one billion dollars. That happens every day with a hot idea.

So, to say that we should have different standards for different drug companies is a thing that we cannot entertain. It just is not on the board here. These things change, we do not have different standards depending on what the size of drug companies are.

One other aspect that was brought up was some priority, I believe Wayne had brought it up,

between the FDA setting up a priority list for drugs that need to be developed in conjunction with COG.

Again, we have to have an even playing field here. We cannot be the arbitrator of saying Johnson & Johnson, your drug is the better drug over Pharmacia. Why? Well, we believe it. It won't go down.

We live by regulations here, and although you here in this committee have a point of view, remember, there is an equal and opposite point of view that will challenge your points of view in a court of law if we overstep our boundaries.

So, I just want to set the kind of the tone of where we have to go with these discussions because we do live within the context of regulations here that have to be obeyed, and the interpretation of these regulations do have some flexibility, but they will be challenged if we cross the line.

DR. SANTANA: Richard, thank you for so clearly articulating the mission of the FDA.

DR. HIRSCHFELD: But I would to just add it is not only the size of the company, but the size of the patient population doesn't merit

different standards either, and it has been the practice in orphan drugs and in pediatrics outside of oncology, where there has been a lot of activity, that the standards are the standards used in evidence-based medicine, and the patients, out of respect for the patients, do not merit a lower standard.

DR. SANTANA: Peter.

DR. ADAMSON: Two comments. The first is in response to Ms. Hoffman's presentation, which I really think touched upon some critical issues, and I wanted to focus on the informed consent.

I think without question, and people on this committee, Rick Kodish and Skip Nelson have shown through studies that our ability to provide informed consent is nowhere close to where we think it ought to be.

The reasons for that need further study and mechanisms to improve upon that certainly need to be developed. What physicians walk is a fine line between hope and false hope, and certainly in Phase I, we don't want to be giving false hope, but we also recognize that our ability to transmit that information in a fashion that families truly understand is quite limited even under ideal

circumstances by very experienced clinicians.

The other point I wanted to touch upon in the presentation is the toxicity and tolerability of Phase I studies. When we have looked at this, Phase I studies in fact carry remarkably low risks of mortality given the patient population, and relative to other things that we routinely do in pediatric oncology, carry quite acceptable morbidity in general.

Part of what we haven't come to grips with as a pediatric oncology community is really following evidence-based medicine for some of what we do. Certainly, I think we are in an era, and hopefully leaving an era, where dose intensification transplantation was applied virtually to every known malignancy or the data to support the effectiveness of doing so is limited and confined to very few pediatric malignancies.

We do that, and it doesn't come under the scrutiny of necessarily cooperative groups or industry, and so forth, but when talking about relapse patients, I think our need for improvement extends well beyond the conduct of Phase I trials.

I then wanted to turn to issues raised by the comments from the public speaker, and I am

sorry, I missed the name, as well as David Emanuel, and that is the issues surrounding intellectual property.

Without question, that has been a major stumbling block for getting agents into preclinical testing, let alone Phase I study. I do want to state that from our perspective, it is very much a two-way street, that we are dealing with our own institutions and their interpretation of intellectual property rights, as well as industry.

However, academic institutions are under some constraints from the National Institutes of Health as far as the ability to assign intellectual property, but having said that, I think industry also is going to have to move off their benchmark, and many industry representatives, in fact, have moved off that and saying no, it is not a two-way street, it is a railroad going in one direction.

We are working with a number of people in this room, with the NCI, with our academic institutions, as well as with COG, in coming up with a master MTA that will be acceptable both to academia and industry when it comes to intellectual property, and when it comes to preclinical testing, I think one can do that.

We are not necessarily playing around with these things in the lab where we may generate intellectual property, but are putting them through what we think will be well-defined studies with clear endpoints and what it will mean.

Having said that, I think industry has to recognize that these are our children. This is not an obscure person. These are our children. We have a societal obligation to these children. I would invite any representative to come and sit with a family of a relapsed child and say it's the lawyers.

So, yes, it is an emotional issue for clinicians and certainly beyond emotional for families. What we want to hear from industry is not that it can't be solved, but how can we go about together solving this problem, and if it takes changes in regulations or legislation, then, let's recognize that and move them forward, but we don't want intransigence, we want a cooperation.

I think that is the intent of industry, and I think the intellectual property issue is solvable, we recognize it is important, but we can't come to the table saying it is not negotiable.

DR. BOOS: I would like to respond to the FDA standpoint a little bit because you asked whether we were willing to accept different standards, and if you are honest, you have to agree that even the FDA accepts different standards.

There are quite significant different standards in developing an ACE inhibitor if it comes, or if you have a new inhibitor drug, more than if you have new ACE inhibitor, you have some thousand patients on Phase III, and with Gleevec, I do not know whether there was even one Phase III trial finished, so you have to accept that the standards depend on the clinical need and on the patient population.

If you summarize what the clinicians today said, then, there is one thing without any doubt. We have a lot of malignancies in pediatrics. We have part [?] malignancy only a few patients. We have established protocols to introduce the new drugs, which means lots of variables, and the amount of variables per patient in pediatric oncology is 3, 4, 5, 10-fold or 20-fold higher than in adult oncology.

If you want to have significant data on such a big amount of variables, then, you have to

be willing to compromise anywhere. This can be the time for development of a product, this can be the level of significance or the power.

What you at the end want to have is safe treatment for children when the drug comes to the market, and the pediatric societies offer this opportunity because we have the networks, we treat the patients in quality controlling Phase III trials. We have the best pharmacovigilance system organized during the last 20 years ever has been organized for a specific population.

Therefore, I would prefer to check specific toxicities for children and some effects, and then open the drug for a short time for one, two, three, four, five years to be just introduced, labeled in pediatric societies and pediatric Phase III trials, not for everybody, just for experienced persons in the concept of a pediatric trial.

Then, you get all the safety data and all the efficacy data you need. The first proof of principle whether or not people are really willing to work on the off-label problem is, for me, whether or not the people in the industry and the regulatory offices would be now willing, perhaps tomorrow, to summarize what has been published by

the Pediatric Societies.

In carboplatinum, for example, there are more than 400 publications in children, more than 200 clinical trials, more than 40 pharmacokinetic observations and more than 5 population-based kinetics, everything in children, and there is no license or no labeling without contraindication in children, and this cannot be the truth, all these data having been published during the last years are not bull shit, they have to be recognized, and they have to be recognized by the companies and they have to take these informations and go to the regulatory offices and say, hey, these are the data and contraindication in children cannot be any longer the proof of the label.

If this does not happen, and we ask several companies with several drugs, I am really in doubt whether they are willing to follow this way.

There was one statement I want to comment on, and this is access to patients in Africa and Eastern countries. I think it would a good step forward if they could have access to the drugs.

Germany is in the position in the middle of Europe that we cooperate very closely to eastern

countries, and these cooperations become more and more effective, and the standards in the eastern countries like Poland, Russia increase dramatically.

They increase because the Western countries support them with experience and with money and with everything, and it is only a short time I think, and then they will cooperate in the clinical trials and cooperate in the drug development trials.

But this is not the major problem, because we do not have lack of patience, as we recognize today we have lack of drugs.

Then, there was one statement that never a drug would be marketed or labeled only for pediatric use. That was your statement. Uricozyme was developed as a drug for palliative care against hyperuricemia in the pediatric situation, specifically pediatric drug development, Phase I, II, and III, and labeling, and this worked, and it worked together with the society sitting here around the table.

DR. SANTANA: Pat.

DR. REYNOLDS: I just wanted to echo some of Peter's comments about the intellectual property

and the statements that were made earlier that that is something that the drug companies won't yield on.

There has to be reasonableness here. The territorial demands that are conceded within the MTAs that we have seen from the drug companies are simply unacceptable to most academic institutions, and they are not consistent with U.S. patent law.

That is where you are right, they do get stuck on people's tables because the institutional attorneys simply will not concede to territorial demands that are simply inconsistent with the normal practice of the institution.

But I think that if the willingness is there from industry to be reasonable, and to come to the table and say, okay, what is fair and what is equitable and what protects their preexisting intellectual property and still allowing the institutions, if they come up with additional intellectual property, to share in that, then, we could all move forward and all benefit from these studies.

DR. FINKLESTEIN: This question is really addressed to my colleagues at the FDA. Part of our charge today obviously, and the charge for the last

few meetings, have been availability and access.

Certainly, we are discussing it here in this subcommittee of ODAC. Malcolm referred to an NCI-COG effort that seemed to attack this, as well. I understand the Institute of Medicine has a cancer subcommittee which is also looking at this. COG has its own industry advisory committee, and we heard that Congress is busy today discussing something other than Iraq.

So, my question really is, since we really are a subcommittee of ODAC, which is really in FDA, does the Agency now have--and this is following up Wayne's comment--enough information to come out with some new guidelines that we can then look at, struggle with, and advise you on?

DR. HIRSCHFELD: Could I ask for clarification? Guidelines about what specifically?

DR. FINKLESTEIN: Well, the challenge today, and the challenge for the last two and a half years, has been drug development availability. The algorithm that is current in force has been discussed by everyone from Pat Reynolds' frustrations to Peter Adamson's comments, and the question is, this drug availability algorithm that is now operational, if indeed it is to be changed,

has enough discussion taken place that since we are a subcommittee reporting to the FDA, that the FDA could come up with some new guidelines for us to struggle with.

DR. HIRSCHFELD: Regarding availability, with regard to preclinical availability, that is outside our jurisdiction. With regard to availability under an IND, that is something we have an interest in, but in general, the availability has been determined by the sponsor, and it has not been in our practice certainly to stand in the way of availability.

We had a program that we endorsed to a product mentioned earlier where there were I will say on the order of magnitude of 15,000 patients who had access outside the clinical trial system, and in general, if we have had a policy, it has been that if someone has access, and this has been tested in the courts, to a therapy that prolongs their life, and they haven't had exposure to that therapy, then, we can withhold permission to have exposure to the investigational--but absent that, we tend to be very open in terms of our policies, it is a supply issue typically in that regard.

I did want to address some other point

that came up, and that was related to the exclusivity question. If I haven't answered you, Jerry, let me know, but someone said that it would be nice if we would grant an exclusivity extension for a negative preclinical screen, and that is not something we are authorized to do. We have to make a decision on clinical data.

If there is a negative preclinical screen in an oncology context, I will point out that it doesn't necessarily exclude getting pediatric exclusivity in another arena.

There are, for example, cytotoxic drugs that are used to treat a variety of immunologic conditions which might be of interest. Many of the signaling pathway drugs might be of interest in hormonal or other inherited diseases, and there would be other alternatives to pursue that avenue.

DR. PAZDUR: Jerry, let me answer your question. You know this committee, what we have to work with. We have the Pediatric Rule. How successful is that? Well, it has its limitations in oncology because we don't have diseases that translate back and forth.

The diseases that do, Hodgkin's disease, acute leukemia, some brain tumors, people in

general or pharmaceutical firms in general are not developing drugs for their primary indications where they are coming in for that disease or those diseases.

Yes, they occur. I could tell you probably 95 percent of the time, we are giving waivers away here for the Pediatric Rule because people are developing drugs in prostate cancer, in lung cancer, in colon cancer. That is what is market driven. This Pediatric Rule works probably better in other diseases.

We have the exclusivity rules, not rules, but incentive programs that apply to us. We have discussed that. Dr. Emanuel asked or said that we should be different in pediatric oncology. Well, we are, and this exclusivity program that we designed when I came to the Agency with Steve and with Mack Lumpkin wouldn't fly in other disease areas.

We are giving exclusivity for sponsors that do Phase I studies that can't go any further because of toxicity. That would not probably exist in other therapeutic areas. We are giving it for negative Phase II data for an attempt at a good-faith effort.

I guess, you know, the question what you are looking for here is an answer to age-old problems of pediatric drug development in oncology, and is it solely an FDA problem, and it isn't.

Therefore, I think we have to take a look at we are only part of the players, and we have certain tools here that we can work with, but how we work with those tools and how much leverage we have with them can't solve all your problems or cannot solve the problems of pediatric oncology.

For example, you know, asking how we could encourage sponsors to introduce agents at the same time they are doing Phase I drug studies in adults, well, I have the pediatric exclusivity thing that I could work with. Does that mean that I could make a sponsor start a Phase I study if they are unwilling to do it? It's an incentive program, it is not obligatory, so I am limited in that aspect.

If you could think of a way that I could make a sponsor do that, that would not come under some type of challenge from a legal point of view, I would be more than interested in hearing from it.

How could we encourage preclinical testing of these drugs? Problematic. Generally, our preclinical aspects focus on safety. They are

toxicology studies, not looking at where the drug should be developed.

Could we somehow bring that into our guidance of a pediatric plan, potentially, you know, have some preclinical studies done before a Phase II program is initiated in pediatrics, that might be a case, but there are certain limitations here and we can't solve all these problems. It is impossible, we are only one piece of the pie here, and I don't want to belabor the point, but I think that we have to focus on what we have available.

The likelihood of me changing Congress is like an ice cube's chance in hell that something is going to happen here, but if you do want that, then, you are going to have to really lobby in that effort, but what we have is what we could work with, and I think that is what we have to address.

DR. HIRSCHFELD: Oh, but just a historical point.

DR. PAZDUR: We have been successful.

DR. HIRSCHFELD: We have been successful. This committee is through an act of Congress. The preclinical development program for pediatric oncology is through an act of Congress. Things can happen.

DR. PAZDUR: But we can focus on what is available and how we could use those within the context of interpretation of existing rules and regulations, but it isn't going to solve everything, there are limitations here.

DR. SANTANA: We have had a very interesting discussion today, and I think it is interesting sitting through these meetings on various occasions, how some themes tend to recur, and I think we are going to have to, at some point, decide how we are going to deal with that, so that we can really get to some of the issues that I think probably will help the Agency and be more fruitful, like the questions or the issues that they have posed to us today.

I would like, with the permission of the committee, to try to start the discussion to specifically address the question that they want our advice on today, which is in this whole issue of drug development, when is the right timing to conduct pediatric studies, what kind of data would be helpful to the Agency, what type of data would be helpful to the Agency for them to make the determinations of whether they do accept or do not accept the pediatric developmental plan when a

sponsor comes to them.

So, I think with that, which is our focus today, although once again, there is a lot of issues that we need to resolve, I don't mean to minimize them or put them aside, but they keep recurring, and I think they are distracting us a little bit from the case at hand.

So, I think with the permission of the FDA, I am going to go ahead and start the discussion on the questions, so that we could really give you the advice specifically that we can provide today.

Questions to the Panel

DR. SANTANA: The first question we have in front of us is--remember that the theme that the FDA wants us to advise is the timing of initiation of pediatric clinical studies in any drug development plan that they may be faced with--so, the first question, and I think that we did hear a little bit of discussion about this earlier today, was: Should adult safety studies precede the initiation of pediatric oncology clinical studies?

I think I will give my perspective on it, and certainly I am going to welcome the opinion of others at the table, I think the answer is yes,

that I think there may be exceptions with certain drugs that for some reason or another we may think will only be developed in pediatrics, in which probably this can be excluded, but those are so rare and far between that those have to be dealt with individually, but as a general statement I think that as a pediatric oncologist, which is what I am here today representing, is that yes, I would like to see some safety studies precede any involvement of myself in a clinical trial for a specific pediatric oncology indication.

Others? Peter.

DR. ADAMSON: I guess the caveat I would have to that is that safety--and I will turn to my industry colleagues--safety is global. It doesn't occur just in a Phase I study. It occurs throughout the entire drug development process.

So, we have to be very careful when we answer should adult safety studies precede. Adult safety studies are the entire development process. Should we have adult Phase I data, I think is probably a better question to ask, and then I would agree that in most circumstances, we should have adult Phase I data.

But I think we heard from Susan and others

that there are going to be circumstances when we don't need and I actually believe in certain circumstances we should have some, but not necessarily complete, because no matter what we do, whenever we start, we are going to have a built-in safety net from the standpoint that the adults are going to get to where they are going before we get close.

So, do we have to wait until their completion? I think in most circumstances, we likely will, but there may be some that we can see biologic activity and we can begin the pediatric trial realizing that adults will go to places that we haven't before we get there.

DR. SANTANA: Susan.

DR. BLANEY: I think that is especially true for biologics or targeted therapy, or whatever you want to call them, because we are going to want to see whatever surrogate endpoint that we choose to evaluate, see a spectrum of dose levels, and that may be different in pediatrics than adults.

DR. SANTANA: Pat.

DR. REYNOLDS: I echo what Peter said. I think that you shouldn't use the term "safety," but the term "Phase I." I think also that we should

recognize that there will be circumstances where we might want to move an agent into pediatrics while the Phase I studies are being completed in adults if you have enough data from the adults to justify safely versus the risk-benefit ratio, which I will defer to Skip to talk about moving it into the pediatric setting.

DR. SANTANA: What data would you advise the Agency that they would need to have in that scenario to allow, not concurrent, but closely concurrent Phase I adult and pediatric studies, how much weight of evidence would you want them to see before they would allow that scenario to go forward?

DR. REYNOLDS: Well, I think that would depend on the particular entity that is being studied. If it is a new molecular entity and you have very little human experience, you may want to have more adult data to make sure there is not something that is really going to come up and surprise you in a major way.

At the same time, if you have an entity that has moved forward and in the adult studies and in the Phase I's early on, you were seeing responses, and there wasn't a whole lot of

toxicity, there may be some compelling reasons to start the pediatric trials fairly early.

So, I don't think we can draw any lines in the sand here. I think there has to be some flexibility built into what we recommend to the Agency.

DR. HIRSCHFELD: Victor, I would just like to clarify the question. The wording of this question is taken almost verbatim from the ICHE11 document, and that document states, "In the case where the disease is predominantly or exclusively affecting pediatric patients," which I think many of the pediatric tumors would fall into that category, then, the document states that the entire development program will be conducted in the pediatric population except for, "initial safety and tolerability data," which will usually be obtained in adults.

That document, we have already signed onto. What we are asking then and what the other questions would follow just to guide the discussion, is for some clarification on what would constitute initial safety and tolerability data, and would it usually occur in adults or were there circumstances where you would consider that it

would not have to occur.

So, the general principle we have already agreed to, it is the interpretation, if there are specific thoughts, that we would like to have those. Thank you.

DR. SANTANA: I will reinstate my comment, which I think I was interpreting this also in the context of Phase I adult data as I interpreted the question, and I will go back to the way I answered it, which is, yes, I would like Phase I adult data to be a part of that, as a major component, before I make my decision about where this is going.

Donna.

DR. PRZEPIORKA: My question then would be, if this drug is actually a targeted drug specifically for a pediatric disorder, how would you ethically justify using it to treat adults.

DR. SANTANA: That was my first answer, then, I did mention that there were some caveats to that and some examples were given on this side of the table, that there may be specific examples like the ones you posed, where the target is uniquely identified in the pediatric population.

I think in that circumstance, I don't think it would be either practical or ethical to

conduct studies in adults before you even have any development in pediatrics, but to me, that would be a very unique and narrow scenario.

As we go along, it may be more and more as we learn more, but right now, to me, that is the caveat to the rule.

DR. PRZEPIORKA: Could I just press the question a little further, if they are sitting in their office and they have an IND show up that is for a pediatric Phase I study and the drug has never been tested in adults at all, clearly, what I am hearing from the clinicians now, which is different from what I have heard in previous meetings, which is we don't care about other studies, other data, you know, kids should be able to get access to Phase I drugs as soon as possible.

I don't think anybody here really wants to do that. I am starting to hear cold feet. But I guess the question is should that be a rule as opposed to let the clinician and investigators decide whether or not they want to proceed with a pediatric study without adult safety data or should the FDA have a rule that says no, we won't accept a study unless we have adult data first.

DR. SANTANA: I will let others respond to

that, but I think it is going to come primarily from the clinicians. If they don't have an interest in it, it ain't going to go anywhere no matter what the Agency says.

Skip.

DR. NELSON: In some sense, my comments are going to sort of lump the first five questions together, but not in specifics. I want to talk about it from an ethical perspective and using Ruth's slide where she titled it, "Timing Access to New Drugs," where she presented from a parents' perspective what they are looking for.

I believe one way of understanding the sort of ethical and regulatory framework, which is for those who are into the Code of Federal Regulations, would be in 50.52, is what conditions should a Phase I trial meet where we would think it is reasonable for a parent to make a decision to enroll their child in that study.

So, it comes down to what evidence do you need for there to be a reasonable assumption of potential benefit. Could that occur in a situation where there is no adult data, where there is only animal data? Possibly.

I know in storage diseases, we have

approved that under prospect of drug benefit, and it has gone forward. Now, I don't know oncology well enough to know if that has ever come up, if it will come up, but I could imagine it could come up.

This notion of safety is really another question of risk, and so as you are looking at that possible benefit, an IRB has to say that the risk and the benefit are justified when you look at them together and are balanced with respect to the alternatives outside the trial, which in this case, since you are talking about using refractory or relapsed disease, are poor, but the quality of life is an issue, so I think Peter's comments about lack of toxicity, all of that will feed into the information you want to have to where, as a whole, you look at that protocol and say, yes, it is reasonable for us, as the investigative community, IRBs is sort of a part of that, to say it can be presented to a parent in a way that we deserve that foundation of trust, if you will, and that we are not taking advantage of the hope that inevitably is going to exist.

The devil is in the details of how a protocol will look. It is sort of in my mind as how I would start to try and answer the specifics

of the first five questions in a technical sense, but that is how I would at least frame it in a sort of broad ethical and regulatory sense.

DR. BLANEY: The phrase came up as to rules. I don't think that there should be any rules, I think there should be guidelines that we follow, but the other issue is a lot of our fear about earlier introduction is not a safety concern.

There is always a concern about treating patients at a dose that is too low to have benefit, and I think that is where we weigh information like pharmacokinetics and exposure from our preclinical models.

But the bigger concern we have about early introduction is the lack of commitment to future drug supply if it is not going to be a drug that is brought forth through an NDA. I don't think that should come into play when we are making guidelines for access.

I think each drug needs to be evaluated on its own merits, preclinical studies, prioritization within the Phase I consortium with the disease committees and the COG, one of the PBTC that are later going to be developing this drug, and those kind of concerns aren't what we should be--yes,

they are concerns that we will take into the process of prioritization, but shouldn't be the primary consideration.

DR. WEINER: But the process of prioritization can't be sort of de facto an assessment of any drug that comes into the FDA, any oncology drug, for any indication.

What you are really suggesting is that there needs to be--and this is something that has been thematic today--there needs to be some sort of mechanism, some sort of forum in which these considerations can be openly deliberated, so that the choices for children and for pediatric oncology and drug development don't depend solely on market factors, on legal constraints, or on communication, for that matter, which is another serious defect that people have alluded to today, that I think is fairly fixable, and would be allied to having the kind of open forum we are talking about.

If it really takes accidental encounters for drugs, you know, in a company, that have activity in a particular disease, accidental encounters with Phase I docs to do something about that, that is not the right way to run a ship that is really going to help the families and their

children.

DR. SANTANA: Jody.

DR. PELUSI: I am also struck by what not only we heard today, but the reading that we were given beforehand. To keep coming back to the fact that a third of the human toxicities aren't even predictable, the question again is, is there a way to collaborate, really move these things through quicker to find some of this stuff out.

Again, I think it is this whole issue of collaboration and really setting guidelines, and not so much rules that cannot be flexible, so I think that becomes very important.

I also think when we are looking at the issue of safety in Phase I studies, is this issue of access globally. I think that we really have to look at that significantly, because that may give us a lot more data quicker.

DR. SANTANA: To kind of paraphrase what I have been hearing, to try to give some message to the Agency in regards to this question, is that I think the pediatric oncology community, first of all, does not want to put lines in the sand that are generalizable, but wants to consider each scenario specifically to the indication or to where

the drug is ultimately going to go and how it relates to pediatrics.

Susan had alluded to earlier today about whether it's an analogue, a biologic, a me-too drug, or a new entity, I think plays a lot into this decisionmaking of what kind of data you would want to see upfront versus how much more data you would want to see upfront, whether it is derived from preclinical or adult studies.

So, I think the consensus that I think we are saying in answer to this question is that, in general--I don't want to paraphrase what Donna said--in general, it is not that we have cold feet, I think in general, it has served us well in the past, and it will continue to serve us well in the past to have some data in front of us, safety in adults with very few exceptions as we think of the applicability of these drugs in children.

But, obviously, there may be scenarios in which we, as clinicians and oncologists, believe that for a particular entity, that may not be so necessary because it is unique to that tumor system or to that target, et cetera, et cetera.

Dave.

DR. POPLACK: I just want to make the

comment that I am not so sure it has served us so well in the past. Just because a drug gets into pediatric studies based on the fact that there have been adult safety studies done before doesn't mean that it is ethical to expose a large population or any population of children to it if there isn't a significant reason or expectation that there is going to be benefit.

I think we have probably done that a lot in the past because we haven't understood the basic biology of the agents and how they work, et cetera.

I think what we might now say usually should be the case, we probably all agree that wherever possible, if we can realistically get adult safety data first, we will feel more comfortable, but I certainly hope that five years from now, that will be the minority of circumstances, because if it isn't, then none of us are doing our jobs properly.

We ought to be using, five years from now, agents that are specifically targeted, as Barry pointed out in his slides, to unique translocations or other targets that are evident in pediatric malignancies particularly.

Therefore, sooner rather than later, we

are going to have to grab ahold of this issue of the fact that we are going to be doing Phase I studies in kids, not only simultaneously with adults, but before, and it may be even exclusively in kids.

We need to be aware of it and realize that it is, frankly, very close to being here.

DR. HIRSCHFELD: May I ask then, Dr. Poplack, what evidence would be appropriate in that case before you would put an investigational agent into the pediatric population?

DR. POPLACK: I don't pretend to have all the answers to this, but I think it would be possible, for example, to construct an algorithm based on a variety of features, and they might include the novelty of the agent, the novelty of the agent as a general anti-cancer agent, novel mechanism of action, then might get a better score if it had novelty that was specifically targeted towards a biologic feature that was uniquely pediatric.

On the other hand, one might take into account the particular illness, so that it may be more feasible to study an agent with a novel pediatrically oriented or specific mechanism of

action if one was looking at gliomas rather than, in the first group of patients, at low-risk leukemia patients.

It would be an interesting exercise, it goes beyond the scope of this group, to actually try and develop some type of an algorithm that might help us sort through those circumstances where we would feel more comfortable in getting started sooner in pediatric studies than later.

DR. SANTANA: Skip, I think you had your hands up first.

DR. NELSON: I am hearing a shift in emphasis, I guess, between issues of safety to issues of possible efficacy, in other words, will you have a tumor response, can you pick a dose, can you design a strategy where you can think it is reasonable to anticipate the possibility of benefit.

So, the safety is still there, but I think it is appropriate to ask what is the evidence you need, which is sort of Questions 2 and 3, how much data do you need to where moving into a Phase I, you think it is reasonable to anticipate possible tumor effect/benefit, and then can you pick a dose that can be used safely as you are monitoring

safety within that Phase I trial.

There just seems to be a different shift in emphasis that the last few comments have made, which I think is appropriate. I would support that shift.

DR. SAUSVILLE: I think it might be possible to begin to construct an algorithm that addresses some of David's concerns. It really builds on a number of the different strains that we have heard today, but also considering some additional issues.

The idea of introducing a brand-new drug into a pediatric population, I agree, I hope we actually come to that point in the near term. That will have been preceded presumptively by the demonstration in an appropriate model that is addressing a pediatric situation, that there is biological activity in the animal milieu along with--and I emphasize this--pharmacology information.

I think then the question that could be fruitfully discussed either by this group or maybe find appropriate expertise is whether one needs to have an animal model that adequately recapitulates the developmental stages that will be most

prevalent in the tumor population.

This was a point that actually was made to me on the break by Dr. Boos, a two- to four-year old's nervous system is not the same as a 16- to 18-year old. So, if you have a drug that is directed to neuroblastoma, you would want to consider whether the safety testing algorithms in the animals beforehand that will get you to that concentration are adequately studied in models that might detect or be responsive to issues there, because when you look back and see why toxicities aren't predicted, there is two basic reasons.

One, we can't score them well. I mean alteration in sensorium, for example, it doesn't take much to be a successful mouse, whereas, obviously, humans operate at a higher level.

The second major reason is that the pharmacology is grossly off for reasons that are trans-species differences.

Okay. So, then you have established that this new agent, in an appropriate model, and this is where I am not sure that beagles and rats and whatnot that we use are adequate here to address all the pediatric circumstances, if you can get to that concentration safely that in other systems

defines efficacy, then, the question is, then, judiciously, in a relatively small, focused study in humans bearing the disease, you try and choose doses that should get you at some reasonable level of confidence intervals to approach that concentration.

Once you have that initial data, it then becomes a fairly simple matter for pharmacokineticists to then scope out a dose escalation scheme. Indeed, Jerry Collins, at this agency, a number of years ago actually proposed a very analogous scheme for adults, which to my chagrin has not been really adopted by many, but probably has much merit to be considered in this case.

So, I think there is a way forward. It is just that it is going to have to be I think more thoughtful than the way that, in some senses--again, this is not my customary collection of colleagues--it is more thoughtful in how the data is applied to the initial experience in this very special population than you may have had previously.

DR. SANTANA: Anne.

DR. HAGEY: Broadly speaking, it is a

sheer numbers issue when you get right down to it. A dose-finding study can take about 30 adult patients, and if you have formulation problems in Phase I and have to start with a new formulation, do another Phase I study, you are talking about 60 patients, which happens quite frequently in drug companies.

Then, I don't want to say wasted, but you have used 60 children, which is about half of what you have available to us per year on a Phase 1 study that may not be the right way to go. If you have at least some dose finding data available in adults, you get a better starting point and thus would use less patients to find the maximum tolerated dose.

DR. SAUSVILLE: But one must be concerned, though. Surely, if the agents are studied in adults, the data would be incorporated, but what about the possibility, the biologically real possibility that there is no basis to study the drug in adults. I mean that is I think the issue.

DR. HAGEY: Yes, that is why I said broadly speaking. Again, there are exceptions.

DR. SANTANA: Pat.

DR. REYNOLDS: I think Ed makes a really

good point, and I think that we should take that into consideration, and the Agency should, in the context of what David says about agents that may be specifically targeted to tumors in the pediatric population that have no adult component.

Are the recommended animal toxicity studies to move an agent into the clinic sufficient for that population, meaning if you are doing studies in adult beagles and adult rats, does that tell you what you need to know if you are going to study it in children.

I think if you have no adult human experience that at least the one thing we could require is that we have good pediatric animal experience. That would be difficult to do, but it could be done.

DR. SANTANA: Bruce.

DR. MORLAND: It is really just echoing some of the points that I think have already been made, but just to say that again, about three or four weeks ago, at a European New Agents Committee in Amsterdam, we debated exactly this issue, and came up with what I hear are broadly similar conclusions about the specific biological agents which will, in the near future, be developed

specifically for childhood cancer and how you evaluate those.

There are a number of relatively simple steps that one would need to do in order to get proof of principle to put those studies into children. It is really is the target there, and there certainly needs to be great cooperation and collaboration within the international groups to build a portfolio of profiles of pediatric achievements, so that there is almost like a directory that you can just tap into and say pediatric Ewing's tumors, yes, they express this, this, and this.

Is that target relevant for the oncological potential of that tumor? There may be some work that will need to be done there. But assuming the answer to those two questions is yes, it is a relatively simple step to them move to introducing the agent, usually in vitro, to show that it actually reduces the proliferative effect. That is simple, that's a couple of weeks work for most people.

But I think, going back to Ed's point, the critical thing for this is going to be having adequate and decent animal models, not just a

xenograft efficacy, which may be the least important here, but it is actually the toxicity information for introducing these agents into children which I think is the critical step, which probably needs more thought than anything else.

DR. BLANEY: None of those models have been validated, and nobody is going to go back to pay--or I sincerely doubt--to pay for validating such kind of models and developing animals for drugs that we use on an every-day basis.

It is going to be stuff that, if that is what we do, we are going to learn information as we go along prospectively, but we are not going to know the meaning of if we give something to a young animal and we see toxicity, we are not going to know if that is predictive of what is going to happen in children or not.

We don't want to set that bar when we don't know what it means.

DR. SAUSVILLE: If I could just respond, I hear what you are saying, and we all like to concept of validation, but as I alluded to, in the data that exists both in a company data set and a separate dataset in our shop, if you regard one-third thereabouts not being detected or

predicted, I could question that, in essence, no animal model is really valid.

So, beyond that, you then create the scenario that you are really trying to find or make the best effort you can to do due diligence to avoid a catastrophic thing that might occur, recognizing that you probably are going to miss the fine points.

DR. HIRSCHFELD: I wanted to share some information and then put a nuance onto the same question.

The information I would like to share is that this entire discussion is occurring, not just within pediatric oncology, but pediatric broadly and what are the predictive models for safety, and what do we know.

The Agency itself has been examining this for many drug classes, because you are only asking the safety question on classes of drugs, not related to diseases, and there is, let's say, a series of examinations of both the positive and negative predictive value of not only the two species of animals testing, but also asking questions about the value and validity of juvenile animals.

There is one arena which we discussed at the meeting on material transfer agreements, and some of the questions that came up is what could be looked at, and we have been looking at the neonatal rat for nervous system, and there seems to be some validation to that at least in some classes of drugs.

I think that would be one area which one could explore in terms of looking more systematically. In terms of if the pediatric oncology community were going to provide--and this is again something we discussed at the NCI--a service to the industry by saying give us your products and we will screen them for you through our screen and look for potential activity.

You could also fold into that general program to be looking at those pediatric-specific safety issues, at least those that can be predicted.

Now, the nuance to the question is if you had an investigational agent that was not pediatric specific, you know, not the PAX1 forkhead translocation or something like that, but just looked at, active and interesting, and Dr. Adamson and Dr. Reaman and Dr. Blaney said we are all

ready, we have patients, give it to us, would you then still wait for an adult Phase I study before proceeding, or would you then proceed?

DR. SANTANA: Malcolm.

DR. SMITH: Let me make sure I understand. If you had some preclinical toxicity data in a pediatric model, would you accept that without the need for adult data even though there might be an adult indication in an adult study that could be done?

DR. HIRSCHFELD: Correct. Let's just say that the adult pipeline is logjammed.

DR. SMITH: We could say that, but I am not sure, it is kind of the converse. What I have seen time and time again and when we have done some pediatric and adult studies concurrently has been the adult study runs ahead, and the pediatric study has to leapfrog, skip dose levels, and so the rate-limiting step on completing the pediatric Phase I study, I think that is the key issue.

The key time isn't when you start the Phase I study, the key time is when you finish it and when you have a Phase II recommended dose for further pediatric study, and what I have seen has been that the rate-limiting step is when the adult

study ends because then you can jack the pediatric dose level up to that, you know, adjust it, and then complete the pediatric study.

There will be exceptions to every rule, and there will be times, you know, Pat pointed out if you are seeing responses in every adult patient that enters the study from the first dose level, why wait with a scenario like that, but in general, if an adult Phase I study is being done, we are much better off to wait for that, to see the complete dose escalation, understand at least at that level what the toxicity experience is, and then make decisions about the pediatric study.

I think the key is being efficient about having our studies ready to go if the agent is really a priority, and then having systems in place that open that study quickly and get it done.

DR. HIRSCHFELD: Just to clarify, Malcolm, the evidence burden would be even if you have the opportunity to do a study before you get adult data, the recommendation would be that you wait until those adult data are available before initiating the pediatric study.

DR. SMITH: Again, I would say if the rate-limiting step, because the adult study is

going to escalate faster, in most cases, you know, that has been the experience, if that is the rate-limiting step and what we are really interested in is completing the Phase I study and having a recommended Phase II dose, in most cases, we are better served by waiting for the adult data, beginning the pediatric data quickly after that and proceeding, and I think the benefits that we learn from the adult experience in terms of informing patients, starting in a dose more likely associated with benefit are substantial, as well.

There are examples where you start the adult Phase I, everything is going fine, and then there is a catastrophe, and that drug is dead. If we start the pediatric Phase I study early, then, we have wasted our time, our energy, and the patients who are enrolled on that study contribute nothing or little to our general knowledge about pediatric drug development.

DR. WEITMAN: I think one other potential scenario, it gets back to maybe a little bit what Anne was bringing up before, is that maybe another potential pitfall, not to be too quick, is that frequently the first schedule that goes into the clinic does not turn out to be the most efficacious

schedule.

I think in pediatrics at least, we have seen drugs that if they don't make it on the first schedule we test in Phase I, it seems very difficult to get excitement built around the drug on a different schedule.

So, my sense would be that there may be another pitfall, if we are too quick to go based on the first Phase I data in adults, and again this may speak to the need for more preclinical work, but if we go with that first schedule, it may not always be the most efficacious, as well.

DR. SANTANA: I think, Steve, we have answered that question I think as best as we could. Was that helpful?

DR. HIRSCHFELD: Yes, it was. If I understand now, unless it is a specific pediatric disease, the default condition should be always to wait for adult Phase I data and then move forward, is that correct?

DR. SANTANA: No. The room over here is saying no, so let's have further discussion of that.

DR. HIRSCHFELD: Okay, let's clarify that.

DR. SANTANA: Greg.

DR. REAMAN: I think one of the issues that really requires the clarification is adult Phase I data using the exact same schedule or if we have preliminary Phase I data from a schedule, have gleaned something different from preclinical testing.

DR. SANTANA: Jerry, you had a very resounding no.

DR. FINKLESTEIN: Well, I just thought maybe at a different voice octave, I could reemphasize what both David and Susan are saying. There are a couple of conditions to Steve's comment.

One had to do with the nature of the tumor. I mean you have neuroblastoma, you have retinoblastoma doesn't occur in a child, I know malignant melanoma may be the same, but it really isn't, so that is one consideration.

Then, David Poplack was pointing out in the next few years, and I am an optimist, that we are really going to have novel targeted, whatever you want to call it, molecular therapy, and we have to think about that.

I mean I could see in acute lymphocytic leukemia, I could see a P190 Gleevec coming out

versus a P210. P190 is pediatric ALL. We are going to target for P190 right away, I am not going to wait around for some adult study.

So, I mean the answer to your question is there are exceptions - molecular and histologic diagnosis. Have I emphasized what both of you are saying?

DR. SANTANA: I think you said that early on, that we all recognize that as this evolves, the exceptions may be the more frequent scenario and more going to, under those circumstances, maybe modify the position that maybe we do not need adult Phase I data before we start that particular pediatric study with all that preclinical information telling us that it is uniquely to that target population. I think we all agree with that, I don't think anybody has disagreed with that.

Susan.

DR. BLANEY: Let me just ask the FDA. Is there a problem with the way the system is working now, because from our perspective, our problem is access. When we have come to the FDA with what we believe is rational information to start a trial concurrently or initially in pediatrics, the FDA has been very responsive and CTEP has been very

responsive in almost all instances.

Are there specific concerns from the FDA right now about the way the system is working?

DR. HIRSCHFELD: Yes. The reason and the entire rationale for this discussion today is that we have been asking for studies without in any way indicating where in a drug development plan the pediatric component should begin.

We have alluded to it. We have referred to the vague wording or what I feel is vague wording, I don't speak on behalf of the entire Agency, from ICHE11. But would like particularly in pediatric oncology to be as specific as possible.

So, if we say do pediatric studies, then, some people interpret that as when they get around to it, and others interpret it when they feel pressured to do it, and then they ask us for clarification.

We have some leverage in this in that if we are talking about an incentive program, we can set the deadline for when that study report should be in. So, if we have a rationale for saying that we feel that there is sufficient evidence to begin your pediatric program, we could set a due date for

those studies to come in. That is a very concrete example.

If we just generically say do pediatric studies, which is what we are saying now, it leaves it open and ambiguous.

DR. ADAMSON: I don't want to add to the confusion, but what I would propose really is building on what Malcolm has said, and that is, in many circumstances, it is most efficient to get to a recommended pediatric Phase II dose when we have adult Phase I data in hand.

I think it would be fair for the Agency when faced with a proposal, to start a pediatric Phase I trial before adult Phase I to say will you arrive at a recommended Phase II dose more efficiently now, and if so, please justify it or please explain it.

If we can do that, then I think that would be sufficient for the Agency to say, okay, let's move forward. If, in fact, the Agency says, by the way, we know there is a proposal forthcoming or there is a proposal on the table here to start an adult Phase I, would you reconsider waiting for that, I think in most circumstances, if we know this is going forward, we are going to say okay, if

they can knock off the first 30 patients in six months and get us five dose levels higher, then, yes, that is going to be worth their while.

So, I don't think there is an absolute answer, Steve, other than saying what is going to get you the recommended Phase II dose in the most efficient manner, and if it is, in fact, more efficient to start the pediatric trial first, then, we just need to provide the rationale and the basis for doing so.

Now, getting back to where the FDA can leverage, and Rick had mentioned this earlier, I think when a drug enters adult Phase I at the latest is when we should be looking at it preclinically, and no, you can't mandate it, but drug companies--and correct me if I go wrong--like to make the FDA happy.

There are guidances, there are rules, but drug companies like to keep the FDA happy.

DR. HIRSCHFELD: Never noticed.

DR. ADAMSON: And if you were to have a guidance or, you know, a by the way that this is part of your pediatric development plan, it would be looked upon favorably if you, in fact, had preclinical pediatric data. My guess is we might

start seeing some agents appear in our preclinical consortium.

That is where specifically I would like to see the FDA help, and I recognize, and I think we all recognize, that the FDA is not the entire solution to all our problems, but I believe it does tie together to the question you are after.

DR. HIRSCHFELD: Well, I am happy to hear that at least we are considered part of the solution, that is already progress.

DR. SANTANA: Skip and then Pat.

DR. NELSON: Just to modify Peter's comment about the endpoint of a Phase II dosing recommendation, I think it is also important in the first child in that Phase I study, that the dose selected has a reasonable expectation of benefit, so you can't start it 10 percent and then go whoops, we can go now to 90 percent. We need to be somewhere in the right ballpark.

So, whatever sufficient evidence is necessary to accomplish that, which I heard could be potentially on preclinical modeling, depending upon the model.

DR. REYNOLDS: Steve, you say that in the context of exclusivity, you can set a date for

report. I presume you can set a date for multiple reports. In other words, you can only have one report, because what I would like to know is why you couldn't require a report on preclinical data for a new agent that is moving forward to be delivered, so that you could force the issue of getting these agents out for preclinical testing.

DR. HIRSCHFELD: Right, we can only address clinical issues, and there is only one report.

DR. SANTANA: Joachim, did you have your hand up?

DR. BOOS: To this point, if you start with a very low dosage because you do not have any experience in adults, and the children expect the chance to benefit, we have to critically discuss the inter-individual or the individual dose escalation, which is a problem I think, but necessary in the situation.

MS. HOFFMAN: To follow that, we have to remember we are a small community and we talk. There are tons of list servs out there, and the parents talk on a regular basis, and if we are giving children a drug on a dose basis and it is not effective, and they are seeing that, it gets

around and it gets around very quickly, and that can basically torpedo other families from wanting to go into maybe a higher dose study. It is amazing, there are thousands of parents on line.

DR. SANTANA: Donna.

DR. PRZEPIORKA: Just from the perspective of an adult oncologist, I could tell you that adults going into a Phase I study also expect that there is some level of hope for activity even at the lowest dose, so I don't know that there is any difference between how you would approach a parent versus an adult subject for a Phase I study.

But to address Steve's question about what is the latest time you want pediatric information, I would think that in your purview as being a steward of safety of drugs in the U.S., that you should have safety data by the time the drug is ready for use in pediatric patients, which is when it hits the market.

If there is a new cytotoxic agent out there that is not specific for a target in an adult tumor, but is rather more broad, I would bet that any oncologist who has a kid with a refractory tumor is going to reach to the shelf for it, and we should have that safety information for them by

that time.

DR. SANTANA: Anne.

DR. HAGEY: I was going to say that it is relatively easy to find a maximum tolerated dose when you are dealing with traditional cytotoxic agents because you treat to toxicity, but this issue is becoming muddied, and it is going to be more difficult than ever to find an efficacious dose given the new agents that are, as Judith alluded to, are in the pipelines of all the drug companies.

I think I agree with her, about 80 percent of the agents in development now are not traditional cytotoxics, in which case it will take more patients than previous to find your correct dose.

DR. SANTANA: Judy, one last comment on this question.

DR. OCHS: One last comment. The other thing, again, I think it is largely pragmatic reasons that you are going ahead with Phase I studies in adults first. There may be exceptions, as David says, but I think the reality is it is going to be more pragmatic, and that is how the drugs are going to get developed.

The other thing is the Phase I, and this was on one of the slides, is if you do find an effective dose range, then, you can get target it pharmacokinetically to achieve the same range in the pediatric patient, and again, Phase I doesn't necessarily have to be an MTD.

The other thing to remember is Phase I is acute toxicity only, and one of the things for me was always the elephant in the room, is long-term toxicity, and that is where some of these models would be helpful, because one of the concerns with some of the newer agents where you are talking about giving them for years and years and years and years is what happens in that situation, and that is where pediatrics again continues to play a unique role in what happens in developing organ systems with truly chronic exposure.

DR. SANTANA: Steve, I think we have given you all the advice we are going to give you on this question. I am making that pronouncement.

So, let's move on to the second question, which is: Should demonstration of activity (emphasis by me) in any (emphasis by me) adult tumor precede pediatric oncology clinical studies?

DR. ADAMSON: No.

DR. SANTANA: Please use the microphone when you answer.

DR. ADAMSON: No.

DR. SANTANA: Any further explanation to the answer?

DR. ADAMSON: I think again if we are starting on a timeline that we are recommending we start, it depends how you interpret this, but demonstration of activity to me means completion of Phase II trials. So, I don't think that should be the bar.

You know, anecdotal report of a patient on the Phase I had a response, I don't think we should use that as information as far as deciding whether to move forward or not, so that underlies my answer of no.

Now, if there is a different definition at work here, then, I might modify it.

DR. SANTANA: Malcolm.

DR. SMITH: As far as the general approach, if a drug is showing activity in 30 percent of the breast cancer patients or the renal cell patients on one of the several Phase I studies that is probably being done with the agent, that is going to be something that Peter and Susan and

others will say okay, that makes us more interested in this agent, and we at CTEP would say yes, this looks like it may really be a drug, and not something that is going to be discarded along the way.

So, I think it is a factor to consider. Should it be a mandate? Well, no, but it can't help but be a factor to consider both primarily in terms of is this going to be something that is going to be available in the long term because it really is an effective anti-cancer treatment for some tumors and rather than just another chemical that we can give to patients and cause toxicity.

DR. SANTANA: So, the answer that you are saying is in general, no, but the information that is provided by those adult studies, number one, will help us prioritize what we want to do because of level of interest, and secondly, it will help us also in getting involved with a drug that ultimately, hopefully, will go somewhere, that doesn't get discarded.

DR. SMITH: It is not a requirement for a study, but is a factor for prioritization, and all things considered, the drug that is showing activity in the Phase I and the company is

enthusiastic about it and proceeding with a range of Phase II studies, that is a drug that there is more likely to be enthusiasm for opening a pediatric Phase I study quickly.

So, it is an important factor, but it shouldn't be a required bar that an agent has to jump over.

DR. SANTANA: Any further discussion on this question? The other question took an hour to discuss, this one took five minutes, so we are making progress.

DR. REAMAN: We discussed a lot of the issues actually.

DR. SANTANA: For the purpose of the Agency, I think we do have to go through the questions. It sounds difficult, but we have to do that.

Question No. 3. Should activity in similar or related tumors in adults precede pediatric oncology clinical studies?

There are a lot of no's around the table. Anybody want to elaborate on the answer?

DR. ADAMSON: I think Malcolm's answer applies. It shouldn't be a bar, but it will certainly influence the priority that we give an

agent, so I don't think it is a separate answer.

DR. SANTANA: Is the Agency content, not happy, content with that answer?

DR. HIRSCHFELD: Right.

DR. SANTANA: This is the one that I think we have addressed during some part of the discussion, but I think the Agency is looking maybe for more specifics on this particular question.

Question No. 4. On what basis can pediatric oncology clinical studies proceed if no activity is shown in adult studies?

I think one of the answer is this whole issue, if it is a drug that is biologically relevant and already we have demonstrated in the preclinical models that that target is relevant to the pediatric condition, then, I think if that is unique to that population, then, I think we should proceed forward.

Greg.

DR. REAMAN: The only proviso would be ensuring that there is going to be adequate supply of that drug or that it is something that is going to complete development.

DR. SANTANA: But I heard Steve mention that there may be other mechanisms that could, in

an ideal world, allow that to happen under the orphan drug or whatever. I heard that answer before, and I want to bring it back.

DR. SMITH: What I heard before, as well, is that this is a situation that becomes society's responsibility. If there is not a market for a drug, I doubt one of the companies on this side of the table is going to proceed in developing it, but it becomes society's responsibility. It is a place where the NCI in the past has done some of the work necessary to get the agent studied further in children.

Right now we have got a Phase III trial in neuroblastoma of an agent for which there is not a company sponsor. We have studied other drugs where the company, by itself, would not have been able to go forward, but in collaboration with NCI, with COG, you know, studies have continued forward.

So, I think there are ways of using public resources, orphan drug resources, NCI resources through COG and others to see that these agents do get some evaluation to whether they are truly beneficial.

DR. SANTANA: Greg.

DR. REAMAN: I didn't mean to imply that

it was industry's responsibility to assure this. I mean whatever mechanism is possible, but that just has to be an assurance, I think.

DR. FINKLESTEIN: Malcolm, I wonder if you would refresh my memory on a drug that industry decided not to proceed with for good industrial reasons, and that the other system of orphan drugs in pediatric oncology has identified it, taken it through completion, and we now use it.

DR. SMITH: Jerry, the two that I was referring to, one is a chimeric 1418 monoclonal antibody that was studied in Phase I actually in adults and children. It was studied in adults primarily in melanoma since that expresses GD2, and studied in children in neuroblastoma.

Phase II studies were done of the chimeric 1418 and now there is a Phase III randomized study as you know. So, that has been done with NCI support both in conducting the study, as well in this case as providing, you know, manufacturing the drug to be tested.

We have collaborated with Glaxo/Smith/Kline in studying compound 506. It is a T cell ALL drug. There is not a huge market for T cell ALL drugs, but we have collaborated to this

point with them in studying this, and have completed a Phase II study for that agent, so I think there are models for how this has worked.

DR. FINKLESTEIN: What I wanted to do is take it historically, one step further and say, all right, that is one part because there is only so much money that is needed to carry out the Phase III study, but do we have any experience in pediatric oncology where the Phase III studies or Phase II studies were successful, and we now have a drug out there that we use in pediatrics because industry gave it up, and we gave it to someone else on a orphan drug basis.

DR. SMITH: No, we don't have that, not that I am aware of.

DR. FINKLESTEIN: I am getting to the point, which is I know the mechanism is out there, but if it hasn't happened in my career, which is 35-plus years, why will it happen in the next five years, and do we need another mechanism.

DR. HIRSCHFELD: I could answer there and give an example in that case, and that is arsenic trioxide where the company that essentially was looking for a product, bought a dataset for studies that they hadn't done, someone else had done the

studies, and they bought the dataset, prepared a submission package, and it got approved, and now it is their product. It doesn't have a huge market, but I think there is precedent for people who want to establish credibility or exposure to sell a niche product.

DR. KODISH: My comment is an effort to be responsive to this Question 4, which is the question of what the basis of going on with pediatric studies are if there is no activity shown in adult studies.

I think I have heard one basis is biologic plausibility. A second is some measure of being able to foresee that there would be an adequate supply, which is what we just were discussing.

I think the third point that needs to be mentioned is that there is the reasonable expectation of safety, and I just think it is important to be explicit about that, and that that safety is in proportion to prospect of benefit to the child, but is one of the important bases, I think, ethically.

DR. OCHS: Actually, I just wanted to bring up a horrible question, what is activity, because I think with some of these newer agents,

you are not really expecting to get activity, whether we define this as response rate or time to progression or survival time, and some of these other agents are not necessarily cytotoxic where you see this kind of activity and rapidity of action.

So, again, it gets to what is the definition of activity. I am grappling with that issue right now about how to define what activity is, and like most things, the answer depends on the question you ask, and you have to ask the right question.

So, I can foresee a situation, for instance, if you did have some agent that there is either a biologic basis or there is some strong rationale and you are not seeing classic responses in a Phase I situation, but it is persuasive that there is activity, antitumor activity in some way, shape, or form going on, that might actually be translatable to another clinical situation, which gets to Jerry Finklestein, that there are those agents that we probably have seen that didn't necessarily show it the way we thought it should show it and that we have dropped.

DR. SMITH: Judy makes a good point about

the trend certainly in the adult world is to look for these alternative endpoints other than objective responses.

I would caution the pediatric setting, though. A child who is six years old with rhabdomyosarcoma is very different from an 80-year-old with prostate cancer. A stable disease or stabilizing disease or slowing disease progression in the latter patient is a meaningful clinical benefit, and is less so in the six-year-old with rhabdomyosarcoma.

I think primarily we are looking for the targeted agents that somehow are able to make tumors smaller, that are able to kill the tumor cells, and while there may be places for the cytostatic agents in pediatric cancer, I think our highest priority, if we are given our druthers, would be to pick the one that actually has an effect, by the effect that it has when it interacts with the target as to cause the tumor cell to die rather than just to stop it from growing.

DR. ADAMSON: Malcolm, the one comment I would put to that, and I think you would agree, is that many of these agents in fact may find a home as synergistic or enhancing agents. So, the issue,

we share the issues with the adults, what is your Phase II endpoint?

We have the same problem in children as we do in adults for agents that, by themselves, are not intended or not anticipated to produce responses, but yes, I agree that these are not agents that we are likely to use as single-agent therapy, whereas, in the adults, they may in fact in certain situations be used as single agents.

DR. SMITH: I modify my comment. The drug that is able to enhance the activity of cyclophosphamide by modifying its target in a favorable way, we are interested in that drug even though, as a single agent, it doesn't have any activity. Good point.

DR. MORLAND: It is a critical issue, this defining of endpoints is going to be very critical for the future with these new biological agents.

Maybe also it is worth reflecting back to--I am sorry to raise it--but Question 1 again, because many of these drugs, you probably will not need to test the toxicity. They are going to have biological endpoints, and as long as you can demonstrate a biological endpoint, you don't need necessarily to go slavishly taking these drugs to

toxicity.

So, I think all of the angst that people were expressing over Question 1, in the future may be significantly less relevant that it currently is with testing standard size toxic agents.

DR. REYNOLDS: Malcolm, with respect to the situation that you described, which is a modulator of antitumor toxicity used in combination, I ask why would we consider studying that as a single agent in pediatrics then? Shouldn't we bring it forward then in the appropriate combination?

DR. SMITH: 0-6-benzylguanine is probably the best example now of an agent that we are studying in combination that we never studied in pediatrics as a single agent, so it is a good point. If there is reason, we have been able to bring a combination forward and get PK data on the investigational agent, and not have to study the single agent by itself.

DR. REYNOLDS: With that in mind, then, couldn't we use the adult data in terms of toxicity to then appropriately design combination studies and move directly into the combination studies in pediatrics rather than going into single-agent

studies first?

DR. SMITH: Potentially. It is like everything, there are case-by-case examples of the agent and its toxicity. My experience, relating to Bruce's comment, is we have got a lot of agents, but I am still seeing dose-limiting toxicities. I mean I think the histone deacetylase inhibitors, there is a target, but yet there is a dose-limiting toxicity that you are getting to when you are modulating that target, the proteosome inhibitors.

I think there are clearly agents that have minimal toxicity at a dose where they are affecting their target, but many of the agents, in fact, have dose-limiting toxicities in the range where they are affecting their target in ways that we think are clinically important.

DR. SANTANA: Skip.

DR. NELSON: Maybe I am a little confused here, but let me just ask a question that has been occurring to me. From the previous discussion about the reluctance to study in Phase I pediatric trials, things that have not shown any efficacy in adult Phase I trials because the drug would basically just stop in its development, it is unclear to me what would then drive the drug into

the pediatric testing arena if, in fact, there is no activity in adults. I mean I am struggling over that basic question.

If we don't do Phase I studies in pediatrics, even in the absence of adult activity, we will never get, if you will, the political or social will to try and find ways to bring those products either under the Orphan Drug Act or through other ways.

I don't intend to open up that other discussion, but I am struggling with how a drug would ever even go forward if, in fact, there is no adult activity given the marketing and economic realities and development realities people were talking about.

DR. SANTANA: Susan.

DR. BLANEY: I think part of that would be based on our preclinical models then, if we are able to validate them and show that activity in our models correlates with activity in patients, if we have an agent that is sky-high on the priority list as showing activity in the preclinical models independent of activity in adults, we would want to pursue it.

DR. NELSON: So, you would pursue that

even if potentially the drug development was stopped on the adult side, and you would be stuck--

DR. BLANEY: Through other mechanisms if we felt strongly about our preclinical model system and its validity.

DR. SANTANA: From what I heard earlier, Skip, was that it is a responsibility of everybody to try to get a solution to that particular problem, and there would have to be both political and social pressure to somehow get the drug supplied.

DR. NELSON: But part of that pressure would be showing activity in Phase I pediatric trials, so I guess if you don't do it, it would be hard maybe to generate that activity.

DR. SANTANA: True, yes.

MS. HOFFMAN: In terms of the toxicity with the molecular targeted drugs or therapies, I mean I don't think we could assume that there is no toxicity because we don't know long term, and it was like anthracyclines, I mean they thought they could give anthracyclines to kids, too, and then five, six years later, you start seeing cardiotoxicities.

We don't know what is going to happen to

the next generation, you know, is there going to be mutations to the germ cells, and these kids will able to produce, but, you know, they will reproduce and have major genetic mutations in their offspring, and I think we just can't assume that, oh, because we don't see an immediate toxicity, that there is not some downstream mutation that could really impact the child 20 years from now or their offspring.

DR. SANTANA: Do you have a comment, Peter?

DR. ADAMSON: I was going to respond that the Phase I study is a very limited study in what it can answer, and what our experience in pediatric oncology is, is that we now recognize that our surveillance for short- and long-term toxicities spans decades. We can't over-interpret the results of a Phase I study. All the Phase I gives us is a starting place to begin the true evaluation of both efficacy and safety of that drug.

DR. SANTANA: Yes.

MS. ETTINGER: I think it would be unethical for us to stop at that point, thinking, you know, looking back and saying well, maybe we will have a long-term sequelae at that point

obviously, and we do have to follow our patients life long. I think that is a lesson we have learned.

DR. SANTANA: I think to the credit of the pediatric oncologists, that is something that we do very well. I think that is an integral part of what we do in terms of both practice and research.

Malcolm, one last comment on this.

DR. SMITH: On this question that Skip was raising about pediatric oncology clinical studies, no activity, I mean the more common situation is that the pediatric Phase I trial does get started, and then sometime while it is being conducted or at the end of it, a decision is made to drop the drug.

So, I don't know if the question, if the FDA wants a comment about that, as well, about continuing studies in that situation, that is really the situation for which we have experience. There, there may be Phase I responses in the pediatric setting or other reason to continue.

DR. HIRSCHFELD: I will just try to clarify. The essence would be what is the evidence burden to move it into the clinic, and once it is moved into the clinic, then, that is a separate discussion.

DR. SANTANA: Somebody mentioned that biological plausibility, if it is a biologic agent, would be something that we would want to know. We want to know something about the issues of safety, clearly, based on the limited Phase I trial that we may have done in pediatrics before a decision is made, and then the third, not necessarily last, but the prioritization of what are the things we have out there that may be important in terms of moving this drug versus another drug forward.

I am going to go on with the next question, but I want Steve to clarify that question.

DR. HIRSCHFELD: Five and 7 are essentially the same question, they are synonymous. We just had two different opinions on how to phrase it.

DR. SANTANA: So, 5 and 7 are the same.

DR. HIRSCHFELD: Yes.

DR. SANTANA: So, we are going to scratch 5.

DR. HIRSCHFELD: May I suggest that you look at 6 next and then come to 7.

DR. SANTANA: Good, we will do that.

The sixth question, which is now No. 5 is:

Potential development plans for new cancer therapies could include combined adult and pediatric studies, another alternative would be separate but simultaneous adult and pediatric studies with continuous information sharing, sequential adult and pediatric studies with information sharing or completely independent programs. So, four possible scenarios.

What are the potential advantages and drawbacks of coordinating adult and pediatric early clinical development?

Malcolm.

DR. SMITH: Didn't we answer this already? I mean in general you want adult data. There will be special situations in which it will be appropriate to either do pediatric first or to do pediatric concurrently, but those need to be well justified.

I think it is the first question, you know, I think we have answered it.

DR. HIRSCHFELD: Just to clarify the question. We want to make sure, not anticipating or not knowing what would come up in the discussion of any of these, that that issue would be presented, because we have discussed it before in

this committee, and it is the theme that we think deserves continual reassessment.

DR. SANTANA: Dr. Reaman.

DR. REAMAN: I think we have made a number of positive comments about some of the parts of this question, but I think one thing we should definitively say is that they should not be completely independent programs, that there has to be communication.

DR. SANTANA: Donna.

DR. PRZEPIORKA: I guess the question comes back down to this just says development plans, not specifically Phase I, so we may be talking about Phase II or Phase III, as well. In those situations, we had talked at previous meetings about some of the tumors are very much similar, but the pharmacokinetics are very different in adults and pediatric patients for cytotoxics, but I am not sure that is true for biologics. I mean even in adults, it is one dose fits all.

So, if Susan has any additional information about whether you think a biologic like a monoclonal for Hodgkin's disease would be appropriate to have both adults and pediatric

patients at the same time, why not.

DR. BLANEY: I guess I don't personally have a lot of experience with monoclonals. I think, however, for the patients with Hodgkin's disease are usually adolescents and older patients, it is not just the younger patients.

So, taking that into consideration, there could be cases when it would be feasible, you know, would be recommended to expedite the development of the agent for the population that could benefit from it.

DR. SANTANA: Donna, I was thinking about some of the recent initiatives that I think COG has been involved with, for example, in melanoma, which is a rare pediatric condition, but certainly our adult colleagues have a lot more information than we could ever get to, but there are efforts of doing combined Phase III trials in that population of patients because it is likely that new drugs and new therapies will be developed along that line in pediatric patients, and unless patients participate in those combined Phase III studies.

So, although the question was for early clinical development, I do agree with you that I think there is going to be an extension to some

Phase III studies, because we have very few patients and the diseases are fairly similar although there may be issues of dosing of drugs that hopefully will get resolved with some Phase I studies that I think we would want to do those studies.

Greg.

DR. REAMAN: That collaboration actually goes far beyond just rare tumors, I mean even into some of the sarcomas, that the rare part of the equation is the patients that are actually being accrued to these trials, because they are adolescents and young adults, and they aren't going on pediatric studies or the adult studies, so there is a lot of collaboration.

DR. FINKLESTEIN: There is experience. In acute promyelocytic leukemia, this is a multi-group approach, and I am sure Donna is aware of that, and we are now trying to collaborate with GOG for our young females who have gynecologic cancer.

So, I think cooperative groups working together is not going to be a difficult task for us.

DR. SANTANA: This issue of APL reminded me of something that I think Malcolm, hopefully, or

Peter can help me understand a little bit better. So, the studies that were done for APL, they were studies that were done together, if I remember those, at least the Phase III study was done together, but the Phase I studies were separate, am I correct, and so there was a different dose that ultimately was used in kids versus adults in the Phase III? Can you clarify that for me?

DR. SMITH: I think the Phase III study was done with the dose of 60/M2 for retinoic acid. Children were more susceptible to some of the CNS effects of retinoic acid than adults, and so there were more problems with pseudotumor cerebri, but I think when you got to the Phase III study, it was the same dose that was used.

DR. GOOTENBERG: Just speaking from a biologic viewpoint, it has taken me a while to get into the conversation here, I wouldn't agree that one dose fits all. We have many examples, one of which I will share with you, where children are unique in terms of their PK with biologics also, and one dose hasn't fit the same adults and children.

I think if you look back at the history, for example, of IL-11, a cytokine which was

originally licensed and labeled and had a suggested dose range for children, and when the studies came out, four children showed an unanticipated DLT of papilledema, and they were unable to demonstrate any efficacy at a safe range in children. I think the label now has been changed basically to say that this should not be used in children. Adults are not just large children, children aren't just small adults.

DR. SANTANA: I didn't want to make a strong statement. I just wanted to say something that goes along with development of retinoic acid and APL, and how ultimately it resulted in a Phase III study in which I think the same dose was used for both populations.

Joachim.

DR. BOOS: In Germany, we try to cooperate with the adult oncologists as close as possible, and I think in situations like myeloid leukemias, lymphomas, or others, it is reasonable that Phase II trials for adults are open for children, too, and children is a broad range of people, as you know, but normally, we then can include more the adolescents, and there is no reason not to do that.

So, I fight with a lot of energy and a

little bit frustrated against the standard exclusion criteria 18 years because there is no reason for an exclusion criteria of 18 years, no physiological, no biological, and no ethical reason.

I think if there are exclusion criterias, a patient with a specific malignancy which might profit from the drug, too, are excluded. This should be an argument, should be written down in the protocol with a specific reason, not the other way around.

DR. SANTANA: Leukemia, in a practical sense, sometimes it is institutionally based because of the population that you are treating. For example, at St. Jude, we may have studies that other people accept patients up to 25 and 30, but with our institution, we cannot enroll anybody over 18, because that is part of the administrative requirement of the institution.

Having said that, I think your point is well taken, that sometimes the age cutoff in terms of 18 versus older, younger adults, that is misnomer, but is not based on real facts.

Dave.

DR. POPLACK: I just think we have to be

cautious about this because even in circumstances where our current biological thinking suggests unanimity in terms of disease biology, we, with more information, may find out that unanimity was not correct, and I think we found that out with Philadelphia chromosome positivity that there are some differences, and as we start using BAC arrays to examine some of these translocations, we are finding more differences.

I think that we just have to be very careful because we can make some false assumptions about efficacy and thinking that we are treating the same entity when we are not.

DR. SANTANA: If you remember, we at least spent two meetings of this committee discussing issues related to that.

Peter.

DR. ADAMSON: Steve, I am going to take a stab at this question, and I agree, we have covered many of the issues, but if we focus the question on Phase I, there, in fact, are potential advantages to having a combined trial, and I think Frank Bayliss, I don't know if he has spoken about it in this committee, has presented some of the advantages.

But if one were to design a trial where adults would start and they would escalate until they hit biologic activity, defined whatever definition one uses, and then the pediatrics would then start and basically would always be following the adults.

The advantage of that trial design is, one, the pediatric study is going to get initiated, by definition, at an earlier stage, but moreover, I think the endpoint that we sometimes arrive to in pediatric trials or even when comparing adult trials, we end up at different endpoints because we have different definitions.

So, we may end up at a different MTD, not because the drug behaves any differently in our population, but we have defined dose-limiting toxicity differently, be it myelosuppression for seven days versus three days versus ever, and if one does it in the context of the same trial, one avoids that.

Furthermore, everyone has their own slant on a modified Fibonacci, and I have yet to see a pediatric Phase I trial where the dose levels were the same as the adults, so we almost never have the same Phase II dose, and it has nothing to do with

how the drug behaves. It is simply who had the calculator and how did you round.

From an efficiency standpoint, from comparison between pediatric and adult populations, there would, in fact, be distinct advantages to combined studies, again with the caveat that we had before, when do you start it, and you would have to build into that trial that, in essence, you have gotten to a biologic active dose. Then, in fact, you are able to move pediatrics to keep in tandem, in step with the adults, one dose level behind.

We have yet to try that experiment, but I wouldn't exclude proposals when there was sufficient data as far as this is relevant for pediatric malignancies, this is a high priority, and we are going to have a trial design that basically streamlines the whole process. I don't know if it will ever happen, but I wouldn't exclude it.

DR. SANTANA: Susan.

DR. BLANEY: I just wanted to make one point. Sometimes they are developed abroad before they are developed in this country, and then the Phase I trials are done in the U.S.

I think that we should be able to build on

Phase I data from foreign sites, and not necessarily have to wait until the Phase I data from the sponsor is this country is available before initiating clinical trials here.

DR. SANTANA: You are talking about specifically pediatric Phase I studies?

DR. BLANEY: Correct. So, if there is data that is available from Japan or France or Germany, wherever, that we should be able to build on that data, and not necessarily wait, if our preclinical evidence is very promising for the agent on the toxicity profile and schedules that we want to support.

DR. SANTANA: Malcolm.

DR. SMITH: To respond to Peter's comments, one is, you know, our primary purpose again for starting a Phase I study is to finish it, and that is I think what we should focus on is does it help us finish the Phase I study and establish a Phase II dose more quickly.

I agree that it would help us to compare adult and pediatric better, but that is not the primary purpose that we are doing the Phase I study.

And the problems that were cited before,

you pick one schedule, it is one of two or three or four different schedules, it may not be the right schedule, and if you wait a while, you could have the pick of which schedule looked like it was best from the toxicity viewpoint after Phase I.

There is the risk when you do that, and the one time that it has been done that I can remember is with CTEC, and there, the pediatric study essentially started once there was biologic activity in the adult Phase I study.

Subsequently, the adult Phase I study had a couple of patients have unexpected deaths from unresponsive hypotension. The pediatric study fortunately didn't escalate to those levels, the adult study was ahead, but obviously, that drug hasn't gone very far since then.

So, you still run the risk when you start early and you don't have the full toxicity experience of studying a drug that, in fact, is going to be not studied any further because it is just too toxic or unsuitable for using in humans.

DR. ADAMSON: Malcolm, I guess in most circumstances I would agree, but there is a false sense of security here, because pediatric trials, as you know, have often escalated beyond what

adults have been exposed to.

So, we have higher MTDs in many of our drugs, so we are willing, as a community, when it is warranted, to take the risks if we believe that those higher exposures may be associated with increased benefits.

So, similarly, you know, the issue here is are you willing to take the risk to expose small cohorts of children when this drug may not, in fact, go on to be the drug. Well, we do that all the time, here, we would be doing it at an earlier stage. But, yes, I agree, I think in most circumstances, we are not going to be pursuing this strategy, but I wouldn't exclude it.

DR. HIRSCHFELD: So, Mr. Chairman, if I might try to capture what I think we have heard. It seems that in all circumstances, there should not be independent pediatric and adult development programs.

So we could then turn to our sponsors when they come in to us and they, say, have a new product they wish to develop or new agent that they wish to see if it turns into a product, we can say that we have brought the issue of having some coordination between the adult and the pediatric

program to our advisory committee, and that they have endorsed the idea that there should be communication and coordination, but some relatedness between them.

I will take advantage of having the chairman of the ODAC here at the table, who I also should compliment, has been a steadfast and continuous participant in all these committee meetings, has been contributing not just her presence, but her expertise and enthusiasm in raising very important questions.

I would then ask Dr. Przepiorka in this same sense, is that something that you would be comfortable that we could communicate to sponsors that we have discussed having some linkage between adult and pediatric plans, and that they should consider one in the context of the other.

DR. PRZEPIORKA: I would say yes, and as I think back over the meetings where the final question that you posed to the committee is should this company get a pediatric waiver, I don't think we have said yes to any of them.

So, you may as well let them know way ahead of time that that is going to be a probability.

DR. HIRSCHFELD: Thank you.

DR. SANTANA: With that, I will address the last question although there was a consensus already emerging that the committee doesn't want to give any hard rule, but rather general comments regarding this issue of within what context would include a general recommendation regarding the timing of the initiation of pediatric oncology clinical studies in a drug development plan.

To paraphrase, to try to give an answer to this, to paraphrase some of the things that Susan Blaney said earlier, I think things that you need to consider are the type of drug, is it a new drug, is it an analogue, is it a biologic, is it a cytotoxic, the mechanism of action of that drug I think would be important.

The safety profile of that drug, I think, and when you know that safety information is important in you deciding when the timing of pediatric studies should be initiated. Then, ultimately, what is the pediatric indication going to be, what is the disease that ultimately is going to have a role in pediatric oncology.

I think with those four general--and other people can add further--I think with those four

general points, I think you can begin to develop a general kind of framework of when you would tell sponsors what they need in terms of initiation of pediatric studies.

I think Skip wanted to comment or add.

DR. NELSON: I would just add sufficient information whether preclinical or adult early clinical to choose an appropriate dose for that testing.

DR. SANTANA: Does anybody have any other comments?

DR. PELUSI: I don't want to lose what Dr. Poplack mentioned earlier was this new mind-set in terms of how we look at what we are doing in clinical trials as things develop.

The question is, is how do we begin to get the message down to the community level especially in the underserved communities that we are, and probably will be, starting clinical activity even earlier in this process, because I think it is an education process not only for us, but for the communities, as well.

So, I just wanted to throw that out, as well, because we are going to have to look at that and what kind of questions will arise in that

community, as well.

DR. SANTANA: Well, as Ruth alluded to earlier, I think there is a greater consciousness at least in the families of pediatric oncology patients, and I think they are always linking to each other, they are always searching and calling different places, so I think at least in the pediatric oncology community, a lot of that already happens.

Now, obviously, the ultimate goal for each parent is whether their child has access to that particular drug that they want to get enrolled on, so I think that is a much different type of discussion because they are interested in finding new solutions to try to cure their kid.

DR. PELUSI: And I think where I am coming from is being somebody in the adult world where unless you do have a child or unless you work in pediatrics, you really don't think about this.

I think that if you are trying to garner support and trying to look at really reaching all levels and getting that kind of support that you may need if indeed regulatory changes come up, legislation, that type of stuff, is that you do want everybody to really start to think about this

and how it will impact everything especially if we are starting to look at global access to clinical trials, I mean we really need to start that.

DR. SANTANA: Susan.

DR. WEINER: I want to make a follow-up comment to what Steve just said and what Dr. Przepiorka just said.

If it is the case that it is the consensus that there needs to be a close collaboration of adult and pediatric direct development programs in the consideration of each new agent, I guess that really places an obligation on each constituency here to make sure that the best data are available to each of us, that is, that the parents have access to the best outcomes, that the companies have access to the best of what academia can offer including the preclinical network, that the pediatric oncology research and cooperative community also tries to work with companies to make sure that the operations are sufficient as possible.

I think that for those drugs that get aborted along the way, that there will have to be novel solutions, novel private or nonprofit solutions that will try to make sure that drugs

that really look as if they only have use in pediatrics will not fall away.

DR. HIRSCHFELD: Could I say orphaned and not aborted along the way, and then they can be picked up and carried through?

DR. SANTANA: Steve, do you have any final comments?

DR. HIRSCHFELD: I would like then to summarize what I think I heard, and that is that pediatric oncology clinical studies should start no later than after the adult Phase I clinical studies are completed, and that there may be circumstances depending upon a variety of factors which we have elaborated on, where one might consider that there is a rationale for starting the pediatric clinical studies without having the adult Phase I data.

Is that an appropriate summary?

DR. SANTANA: Yes.

Malcolm.

DR. SMITH: The phrase "should start no later," I can't say that. I think generally, should start at the end. I think there will be situations in which we will want to see all of the Phase II data before we are convinced that this is really something that is good for pediatrics.

I think generally, you know, at the end of Phase I is a good time, but there are agents for which we are going to want to see more information before we are convinced that there is a sufficient body of evidence that this should be studied in children.

If that is available at the end of Phase I, fine, but it may be that a larger body of evidence needs to be developed to convince Peter or Susan, and others that the drug should be studied in children.

DR. SANTANA: Peter.

DR. ADAMSON: Steve, I know you can only comment on clinical, but in the spirit of keeping the Agency smiling, I think it is fair to say that the new agents should be made available for preclinical study in pediatrics no later than when they enter Phase I in adults. Recommended.

DR. HIRSCHFELD: Peter, I would like to say that I think we have been smiling from the first moment that we got the acceptances from everyone here that they were willing to participate, and we anticipated, and I think we have received, a very thorough and thoughtful discussion on this issue, and I think from where we

started this morning until now, we have made I think an enormous amount of progress in clarifying important issues, not just related to this question of timing, but to other critical questions related to pediatric oncology.

I thank every one of you and also think that we can all be very proud of what we have accomplished today, have accomplished in the past, and anticipate we will accomplish in the future.

DR. SANTANA: My thanks also to all the participants for a very professional and very high quality discussion, and we will consider this meeting adjourned.

DR. HIRSCHFELD: I am sorry, I want to announce the next meetings. We will go on a cycle to coordinate with the general pediatric committees, and our next meeting will be February 10th or 11th, 2003, and the meeting after that will be the second week of June 2003, and then there will be a meeting in October 2003, probably the third week, and we already have selected some themes and questions for the meeting in February, and as soon as we have those adequately refined, you will be hearing from us.

[Whereupon, at 3:50 p.m., the hearing concluded.]