and most of them are the letters and number agents.

We have primarily focused on the targets that are in the cancer oncology world. I didn't bring a list of the targets but, if I had it, you would recognize the receptor tyrosine kinases, BCL-2, HSP-90, histone deacetylase inhibitor. So the things that are primarily in the clinic, many of them in the pediatric Phase 1, are moving to pediatric Phase 1, so about 10 to 12 agents per year.

In terms of hits, if you will, you know, where we say, ah, this looks really interesting, I think there are several. Some I can talk about, but, you know, ABT263, the VCL-2 inhibitor from Abbott really looked quite interesting, and the ALL panel. So that would be something that we would be quite interested in and have had discussions with the ALL Disease Committee and others in this room about how can we move that into the clinic and discussions with Abbott, of course, about that.

So, that is one. It is not broad, it's the ALL panel, but very good activity there. In retrospect, our data were necessarily needed to drive the IGF-1 receptor antibody story. But we did see activity in the Ewing sarcoma xenograft I showed. We saw activity in the

osteosarcoma xenograft and so I think that helped stimulate some interest in that area. So those are going forward.

Then, one agent that we presented at just at AACR a couple of days ago was Namura-A [?] kinase inhibitor, which actually was quite effective against the neuroblastoma panel, which is our most refractory panel, and that was the most--and the ALL panel. But those were our most responsive panels.

Again, those are ones that we are interested to move forward with both in the neuroblastoma setting and ALL is hard, but there, as well.

DR. S. MURPHY: Did I hear you say that you have moved some of these lettered and numbered agents into the Phase 1, that they are already in the Phase 1, and now you are putting them through the panel?

DR. SMITH: We had a backlog. You remember we started only testing about 3 1/2 years ago. So there were some things that were in the clinic already and we were trying to catch up on them.

DR. S. MURPHY: Why would you do that?

DR. SMITH: Well, one of the things, you know, a Phase 1 decision again is an easier decision to make. You

know, where you go after Phase 1 is a harder decision.

Having data for some of the agents that Peter and others in the COG Phase 1 Consortium or the VBTC have been studying doesn't help with Phase 1 go/no go decision. But it does help with what you do afterwards.

DR. LINK: I have just a couple questions that are actually addressing the two opposite sides of this. One is that we have actually had--first of all, your notion that some of these agents should really give you CRs in a xenograft model really cures, yet, in some of these agents that have proven to be very effective, especially novel agents now, biologics, look like you get stable disease, you get stable disease for a very long time.

So, the question is whether those, when added may be helpful. And the opposite is also true, that we have an experience in rhabdomyosarcoma, as you well know, a frustrating one, where the agents were super-duper in both the preclinical testing, in the Phase 2 testing, window design, whatever you want to call them and the response rate was astonishing.

But when you put them to the test in a Phase 3 to add to what we have, they were pretty disappointing. So the

question is, you know, how much should we bank on this, because you may be wrong either way, you may be wrong that an agent can stabilize disease for a long time may be helpful and also that an agent that causes great responses may not actually add anything to what we already have.

DR. SMITH: We will be looking at agents--I mean, we have seen plenty of agents that slow growth and that may have benefit, and certainly studies are going forward in the clinic with agents whose primary effect will probably be to slow growth by an anti-angiogenesis mechanism. So that is going forward in the clinic and it is possible that that will have the effect that--you know, it is possible that that will have more than a delay in time to event.

I mean, what we are really interested in, right, is improving survival and not just delaying time to event.

DR. LINK: The mTOR story is a good example of something that you would have not essentially jumped all over based on its single agent preclinical stuff.

DR. SMITH: So, we are looking at some combinations like that. I mean, it's a good point. There were some data that would suggest that mTOR might be good in those combinations. But I guess one response would be just

the lack of single-agent activity or modest single-agent activity doesn't mean forget about it but have a good reason for the combination, work you are going to do and for what you are going to think is a success from your combination work.

DR. ADAMSON: Malcolm, let me first begin by commending you, because I think you and Pete and family advocates have really shepherded it through a remarkable process, and I am hoping that, in the next five years, because it is still an experiment, we will begin to answer what the predictive value is. But it has been an extraordinary story to date and you are to be commended for that.

With all due respect to everyone who has presented here, the most compelling slide I have seen today was Lisa's. And I think it is your data, that over the last decade we have not impacted mortality from childhood cancer.

That ought to serve as a very loud wake-up call to everyone involved with the care of children with cancer because childhood cancer has been touted as a success story, truly a success story. That is going to fade. That is going to become a historic event if this plateau is

maintained.

I am going to turn to your comment about opportunity cost. I agree with virtually everything that you presented. But I think the other cost--and it has pointed out the correct term--but it's a timeline cost, that we are in a situation that we are never going to have sufficient data to make decisions that are risk-free and where we say we are ready to take the risk--that bar for Phase 1, I think you probably said it is pretty low. For Phase 2 it's somewhat higher. And for Phase 3 it's at the highest.

But without question, we can't continue to do business like we have been doing business at really every juncture. Our timeline, as you have pointed out, are remarkably long and you are only showing the timeline from when we start the trial. You are not showing the timeline from when we propose the trial.

You can probably add at least three years to Phase 3 from this is a great idea to when the trial started. Those numbers are somewhat misleading and so that plateau is, I think, alarming and I think it should call all of us to rethink how we are going to move forward because the old

paradigm, which has dramatic success, is clearly a paradigm that is not continuing to bring success, and I think the evidence is presented today.

DR. SMITH: I agree. It maybe gets to Michael's point as well, that, you know, where some of the new combinations that we have brought into the clinic are killing the same cells again, and it's the ones that we can't cure, we don't have the agents to go after those.

It is new treatment approaches, it is understanding biology, the drivers and the biology and, again, a data-driven process, the tools are available now to do so much more than we did nine years ago, it is astounding.

DR. S. MURPHY: This may be a little bit editorial, but I was triggered by one thing you put up there about how agents get added or tested in children. It was the example of rituximab added to lymphoma treatment.

It is related also to your slide that you had on the various patient subpopulations and niches of kids that you have identified. The point I am trying to make is we really need some--I kind of agree with Peter--we need some totally different out-of-the-box ways of clinical trials

designs, which we haven't had any discussion of yet.

It seems in the adult oncology circles, there is lots of robust discussion about novel trial designs in early drug development and we are kind of stuck in the same old pyramid that you have got there.

To my way of thinking, this rituximab story, you know--even when I was group chair, this was percolating up--and the problem there is to show that rituximab gives a significantly superior contribution to already curative therapy would take more patients than there are in the world to show a benefit. What has happened I am afraid is you can show that you can add adult drugs or other targeted drugs or something and that it is feasible.

Of course, it adds to the cost of treatment hugely. But what we haven't shown is that then you could take away some of the very toxic alkylators or anthracyclines and have a better, you know, tolerated better outcome for the children.

I reject the rituximab-plus intensive B cell therapy as being a great success story. I see it as like, well, there we go, hoodwinked again, what have we done now, and I am a little worried about showing that it is actually

adding something.

DR. LINK: Well, the design for the study is actually proof that you can take away the anthracycline. So you will be happy to know that.

DR. S. MURPHY: I will be happy.

DR. LINK: It hasn't been launched yet.

DR. S. MURPHY: How long will it take? That will be another, you know, how long. Years.

DR. SMITH: It is a good point, though, that NHL is one place, you know, the B cell, you know, where the outcome has really improved.

DR. S. MURPHY: But the issue is I think we need some trial --

DR. LINK: There is not a single new drug than LMB89 that wasn't available when I was a resident.

DR. S. MURPHY: I don't know that there is an answer to the points I raised. But we need more research on new trial designs or better ways of designing these early drug trials to use fewer patients and get done in a faster time and have something firm about it, I think.

DR. BLANEY: I mean, I agree with Sharon's point. I think our route to approval has always been overall

survival or progression-free survival, whatever, but our success does come at a price of long-term toxicity. So, as we get new agents that are potentially theoretically less toxic, our endpoints are going to have to change, which is even a harder challenge to do non-inferiority trials.

As we make an orphan disease and sub-classify it, we have greater challenges. So we do need new paradigms and thinking that is really out of the box.

DR. REAMAN: Just to extend that, those endpoints are not early endpoints. So the five-year timeline for study conduct, if the endpoint is really late toxicity, is only going to compound our current problem of being able to do studies in a timely fashion and answer questions.

DR. CURT: One of the things we did discuss in the Life Sciences Consortium was the role of the NCI in setting priorities in this area, which we felt could be considerable and we discussed this largely in the context of incenting sponsors to provide compounds to the NCI screen.

I was just wondering, Malcolm, how routinely do sponsors approach you for early signals for activity in drug development and is there anything that you think we could do to improve that.

DR. SMITH: It has been very gratifying to date that we have worked with a number of different companies, many are coming back for a second or a third agent at this point and so, knock on wood. But to date there are companies that have really interesting agents with novel mechanisms of action have been willing to work with us.

If that becomes a problem, then we really need to address it and identify what it is, what the concerns are. But to date, you know, we have had companies coming back to work with us and had companies contacting us about the program.

DR. LINK: For pediatric only?

DR. SMITH: This is just pediatric.

DR. S. MURPHY: This may be a question for Dr. Pazdur, because just to pursue this point about novel trial designs and less time to drug approval rather than waiting until you have overall survival, brings up the question of surrogate endpoints as ways to pursue drug approval, accelerated approval and then have opportunity for definitive studies later.

This is controversial I understand, because a correlate does not a surrogate make. But we had--in

pediatrics, I think we have evidence, which we went over at a workshop that ASH and FDA had, at least in leukemia, that minimal residual leukemia--and monitoring this is a good surrogate for overall CR and survival, we think--some of us, me especially, think the evidence is compelling for this and it would be a great way to get early signals for new targeted anti-leukemia drugs, that we wouldn't have to wait until all Phase 3 studies are done to show improved survival.

But the position, maybe you could restate what your position is on this, because if we ever want to bring drugs to market faster, we are going to have to come up with smarter ways of identifying activity.

DR. PAZDUR: Well, I was going to present this material after the presenter is going over our approvals that we did in the Office of Oncology Drug Products, and would this be a good time for me to do it now?

It really answers your question about the use of surrogate endpoints or other endpoints other than survival. It also I think points out to some very important numbers and concepts and here again I did this project and I wasn't planning on presenting it. But some of the issues came up

during the presentation. I don't have all of the data with me particularly with regards to pediatric studies, but I just wanted to give you a gestalt feeling.

We did a project in the office looking at when the office was formed in July of 2005, and then all of the approvals of new indications, both new molecular entities and supplemental entities to December 2007. So that was a two and a half year period of time.

These included drugs in the Drug Oncology Division, the Biologic Oncology Division and Hematology Products, which are in our third division, benign biology products, such as iron overload, drugs for erythropoiesis, et cetera, so there were--well, let me ask you. How many do you think there were?

There were actually--and this is surprising, and I think most of us were actually surprised, because of the activity in adult disease and most of these obviously were adult indications.

You know, if you hear our naysayers out in the FDA bashing room, it would seem that nothing could ever get approved by the FDA. But, during this two and a half year period of time--and oncology is one of the most active areas

for pharmaceutical firms--there were 53 new molecular entities or supplements approved during that period of time, so a considerable amount of activity, and these were new indications.

Of those 53, there were 18 new molecular entities and 35 supplemental applications, so considerable activity; 39 of those were priority reviews meaning that they were approved within 6 months, 14 were standard reviews, which was a 12-month period of time. There were 38 full approvals, 10 accelerated approvals, 5 applications that were accelerated approvals previously, were converted to full approvals, indicating to us that this accelerated approval system is working here.

But getting to your question about what endpoints, if you want to take a look at these 35 new indications, overall survival was the primary endpoint in 10, disease-free survival 5, progression-free survival or TTP in 12, response rate 17. Others were 5, and those included like reduction of iron or reduction of extravasations, et cetera, since some of these were also supportive care products.

Let me ask you this question. During this same period of time, because you hear so much negativity coming

out here, how many products did not get approved by the FDA during this two and a half year period of time? Guesses? Five. There were 5 not approved, 4 of them missed their primary endpoints, had negative trials basically, and 2 were withdrawn, 1 for manufacturing reasons and 1 other one because of problems within ODAC, which I believe the sponsors realized that they were going to get an NA letter.

The other important things that I want to bring to your attention is that there were many drugs that were approved for rare diseases and we are going to be publishing this data. Here again, I don't have all of the data here.

But there were drugs that were approved for dermatofibrosarcoma protuberans, myelodysplastic syndrome, systemic mastocytosis, hypereosinophilic syndrome, refractory Philadelphia-positive pediatric ALL.

DR. LINK: That is all one drug so far.

DR. PAZDUR: I will get to others. I will get to others. PNH, cutaneous T-cell lymphoma, mantle cell lymphoma, neoplastic meningitis, extravasation, several for GIST. There were diseases. I think these are noteworthy during this period of time and even shortly before that.

Diseases, there were really very suboptimal

therapies, and I am pointing to renal cell carcinoma whereas a decade ago the only drugs that were used were basically interferon and now there are three drugs and several others coming down the market.

Drugs for CML, imatinib, and its subsequent drugs, hepatocellular carcinoma drugs were used for, so a lot of activity here. If one takes a look at the drugs that were not approved again, basically, these were drugs that we brought at ODAC--and one of the reasons why we want to present this data, and we will be presenting it in a written form, is that generally we have taken the drugs that are problematic to the ODAC. That is what most people see and think about are several examples.

It takes us a considerable amount of time and effort to prepare for an ODAC meeting. We don't have any PR department or people to help us with slides. The medical officers have to make their own presentations, they have to make every single slide. They have to practice. This takes our effort away from other activities so we are very select on what products we take to a public forum.

The drugs that we have had prior discussion on, endpoints, et cetera, and have agreement with the sponsor,

we generally don't take, and I think that is why many people really don't have a good picture of the activity of this disease.

Sharon, getting back to your issue, we are not demanding overall survival. If you take a look at these 53 indications, only 10 had an overall survival, 17 had response rate and I think we would be open. Here again, I think what is, you know, the magnitude of effects that you are seeing here also on an endpoint really plays into part here.

So, again, the purpose of kind of this brief presentation is to kind of give you a flavor of what is going on and really a need for some priority here, because there are a lot of drugs that are coming down the pike here and there is a need for either larger studies or larger--not larger studies--but greater accrual. One could go through multiple agents and look at multiple drugs, but the activity is definitely there in an oncology field.

DR. S. MURPHY: Thank you for that summary. But, as I heard it, true you are not just using overall survival. But all of the approval endpoints were clinical and there were no--at this point, no surrogate endpoints.

DR. PAZDUR: Many people would argue that response rate is a surrogate, PFS is a surrogate.

DR. S. MURPHY: Some would, but I was talking--well, okay, uh-huh. I am thinking more of biomarkers.

DR. PAZDUR: I think part of the critical path initiative is to take a look at these endpoints. But one has to ask themselves when one is making a regulatory decision, how much confidence that you have in that endpoint, it is free of bias, correlates with some clinical meaningfulness here, it is not just purely a laboratory parameter that one is dealing with. There are a lot of factors that require an academic buy-in, not of one person or one group of people, that's for sure.

Also, I would like to point out one of the other issues in talking about this whole internationalization is part of this effort also is I think to bring us into some closer alignment with the EMEA. The EMEA has traditionally taken a look at PFS as a primary regulatory endpoint for approval of drugs.

As you can see from some of our more public approvals recently in breast cancer, there has been a move toward the agency to accept that endpoint, bringing us into

closer alignment.

DR. ADAMSON: A quick question for you, Rick, and one for Karen. The question has to do more with our drug discovery output. Of the 18 NMEs that you spoke about, how many were first in class, do you know?

DR. PAZDUR: I would have to take a look at that.

DR. ADAMSON: Any estimates of what that would be?

DR. PAZDUR: No.

DR. ADAMSON: My question for Karen, and it leverages a comment you made, Greg, I think one of the reasons the preclinical program has been successful in engaging companies, well, two of the reasons, one, I think it is low risk to a company because, if we discover that your drug is not active in Wilm's tumor, you are unlikely to take a major hit as our announcing we think it is going to be inactive in colon cancer. So it's low risk.

So, my question to Karen, the other argument I put forth when talking to companies to engage Pete and Malcolm, is that there is value to this data, positive or negative, and the negative value may be--as the pipeline fills up for Phase 2, we may rely on this and to lessen the priority for an agent and, when it comes to PREA then, if we present

evidence to say we don't want to study this in these disease indications because the evidence is leaning against it, is that a fair argument to make when you consider the PREA requirement says if the pediatric oncology community believe it has evidence that it is simply not going to prioritize, that a company might utilize that information to say, okay, you know, we can't meet your demand here?

DR. WEISS: Yes, I think that if there is enough evidence to suggest that there would not be some kind of meaningful therapeutic benefit, MTB, then, I think one could probably make that argument.

Right now people are just kind of I think interested in trying things because you just don't know, and it would be nice to get to that point where you could say, no, this drug doesn't seem like the best choice, this one seems like a better choice for whatever body of evidence that you have. So I think that that would be something that--you know, I don't think we have had an experience specifically in that type of issue but I see it coming and I think it would be appropriate.

DR. D. MURPHY: And we have had it in other areas of small populations, limited populations where products

have come and we have said we are not pursuing this product by any mechanism particularly sometimes the sponsor wants to pursue it, pursue it under the exclusivity and we have had some very contentious discussions.

Again, this internal committee, sometimes the division will have to come back and forth a couple times, and we will say why we don't think we should pursue it. And it gets to, you know, particularly those orphan or limited populations for products and in a way we are prioritizing.

DR. LINK: Let's go on to the next presentation, it's the last scheduled presentation, and then we will have time for more discussion at the end.

Dr. Reaman. back to sort of the theme for the day, which is we have come a little far afield, which is our international collaboration.

Overview of Pediatric Transatlantic Studies

DR. REAMAN: Thanks.

[Slide.]

I will go through this relatively rapidly, hopefully because some of this is obvious and some of this has been said and presented in other venues. But, as far as international cooperation from our perspective, I think the

case statement can be made by virtue of the fact of the limited patient numbers, particularly, the need for expanded Phase 3 study populations as we continue to subclassify patients and make what were common diseases, now even more rare disease types with particular and potential molecular targets, access to new agents and the need for communication and globally prioritizing.

[Slide.]

Perceived historical barriers, I guess I should call these borders following Dr. Lumpkin's presentation, but in the past, cultural and health care delivery differences, how we actually collaborate, what constitutes a collaboration is it participation in one group's study, is it actually collaborating in design and conduct, and who coordinates that study.

Compliance with GCP guidelines and assurance that those guidelines are, in fact, being met, has been a barrier, it continues to be a barrier to some extent. Whether or not the international collaboration is going to be accomplished through a single institution, through a consortium of institutions, or through a recognized cooperative group or established group.

The other problem or difficulty challenge has been informatics and harmonization of informatics related to data capture, specific electronic platforms, language and data-management analysis and reporting.

[Slide.]

Access to new agents and their distribution internationally. Correlative studies has also been somewhat of a challenge as we talk about biospecimen acquisition and transfer and analysis and whether that analysis is going to have impact on patient management.

Certainly funding variances between international groups have created challenges for whether we can do studies internationally and regulatory requirements, their inconsistencies, and seeming inflexibility.

[Slide.]

Despite the challenges, I think everyone thinks that COG is a U.S. group or a North American group and, although we are based in the Unites States and, in large part, supported by the United States Federal Government through the NCI, we are strongly represented internationally with 17 study sites in Canada, 8 in Australia, 3 in New Zealand, 3 in Switzerland, 2 in The Netherlands and we are

contemplating 2 study sites in Mexico and eventually expanding that to 5.

Only in Canada have we actually been required in recent years to develop in compliance with Health Canada regulations, a designated individual who resides, works in Canada as the sponsor for clinical trials that we do in COG. That individual is also responsible for working with Health Canada in obtaining no objection letters for investigational drugs or unapproved drugs that are imported in Canada specifically for clinical research.

That has actually necessitated changes to our institutional audit program, our pharmacy audit program, because there are very specific Health Canada requirements for how investigational imported drugs or drugs imported for investigational use are labeled and handled by pharmacies.

[Slide.]

Just to talk a little bit about three examples of studies, and I think these were our earliest foray into the market, if you will, as far as international collaboration: an early study in non-Hodgkin's lymphoma, our participation in the EURO-Ewing's study and, finally, a major massive international collaboration in osteosarcoma, the EURAMOS

study.

[Slide.]

So, the CCG, this actually preceded in design anyhow and in negotiation that preceded the merger and the development of COG was a collaborative venture of the Children's Cancer Group, the French Group, and the UK Children's Cancer Study Group, which opened in May. This was for B cell non-Hodgkin's lymphoma. It accrued some 1,200 patients over 4 1/2 years.

Basically, this international trial was done so that each individual group had responsibility for data collection and management, however, there was centralized data analysis and outcome and review and, because each individual group was responsible for its own data collection and management, there was no requirement for federal-wide assurance numbers outside of the United States and Canada.

This study was actually coordinated by the UK's Medical Research Council.

[Slide.]

The EURO-Ewing's was also relatively easy from the standpoint of logistics in that CTEP approved COG's participation in an existing European trial, and our

involvement to include enrolling metastatic patients only with a randomization to intensive chemo versus high-dose therapy and stem cell rescue.

We were purely participating, there was no U.S. coordination. This was all coordinated through the University of Muenster, which fortunately had a federal-wide assurance number from OHRP and permitted our proceeding in participating in the trial.

[Slide.]

EURAMOS was a little bit different. This included study sites and study groups in Canada, the U.S., Austria, Belgium, Denmark, Finland, Germany--they are all there. More than 200 European centers in the more than 200 centers of the Children's Oncology Group.

It was anticipated in the beginning that nearly half of the projected patients would be non-COG enrollments, and the European institutions committed to comply with the European Commission Directives, The European Parliament and Council and ICH-GCP standards.

One of the difficulties in our initial negotiations for study design and conduct was the development of an external Data Safety Monitoring Committee

rather than the people involved in actually conducting the study being the reviewers for severe toxicities and unanticipated adverse events.

[Slide.]

There was agreement that relevant European and American laws would be observed to ensure human research subject protection and this would include ICH-GCP standards, would certainly include independent ethics board approval.

Where we actually began to trip up was the concept of equal partners and no right for a single group or a single country to impose local regulations.

So, this became difficult for us from the standpoint of NCI and CTEP approval to participate in this study without making sure that each of these 200 European institutions had to have federal-wide assurance numbers for which there was outrage on the other side of the Atlantic.

So, with presumably sufficient safeguards, we proceeded in actually negotiating that the FWA, Federal-Wide Assurance number requirement could be held by just the coordinating center rather than all of the participating European institutions. And we did convince our colleagues that they had to develop an on-site auditing program that

would be acceptable to CTEP.

So, again, this study was coordinated by the MRC.

[Slide.]

Some other logistical difficulties with this was that there was an investigational drug that was part of this study. COG holds the IND for this agentand, despite that fact and despite the fact that it is an agent that is supplied here by Schering-Plough, it is distributed in Europe and Canada by other corporate partners and that actually has presented no problems.

The accrual is very much ahead of projection and, in fact, there are discussions underway for follow-up studies that again would include these existing international groups and perhaps others.

As far as other international participation in COG trials, the Dutch Childhood Oncology Group, basically all 7 academic pediatric cancer centers. In The Netherlands, we have a negotiated clinical trials agreement between COG and the DCOG for them to participate in studies, and they are currently enrolling patients on NHL studies, brain tumor studies and Hodgkin's disease.

Their coordinating center in the Hague where their

headquarters are basically receives, manages, and transfers all of their data to our data center using our electronic remote entry system.

We have a similar agreement with the Israel Society of Pediatric Hematology-Oncology and 6 academic pediatric cancer programs in Israel with a coordinating center at the Schneider Children's Hospital. Both of these have FWAs at SKION Headquarters, as well as Schneider Children's, and they coordinate all of the data management for Hodgkin's disease trials and brain tumor studies that these Israeli centers are participating in.

We are just beginning to activate a study for adrenocortical carcinoma with the two single institutions, two very large institutions in Brazil, one in Sao Paulo, one in the outskirts of Sao Paulo.

Each of these institutions do have FWAs. They will be participating as single institutions. We have trained data managers and have sent Portuguese-speaking data managers to Brazil to assist them in utilizing the same electronic data entry system for transferring their data to the COG data center.

[Slide.]

Some pending international trials. The JP Garrahan Children's Hospital in Buenos Aires will be participating in a multi-agent, high-dose therapy with stem cell transplant rescue in extra-ocular retinoblastoma.

We are looking to enroll patients on all of our retinoblastomas from two huge institutes in India, one in Hyderabad and one in Chennai, each of which see 200 to 300 retinoblastoma patients a year, so this is addressing the issue of small populations for Phase 3 studies.

We are in the process of developing an agreement with what was formerly the Medical Research Council's Leukemia Working Party, now part of the merged UKCCLG with the coordinating center at the University of Birmingham to participate in a Phase 2 study of Lestaurtinib, a FLT3 inhibitor in relapsed AML.

So we have had a significant history in international collaboration including clinical trials involving newer investigational agents.

Clarifying Questions from the Committee

DR. LINK: That was great, Greg. I don't know the right people to ask this of, but I read through the presentations and everything from I guess it was 2003

meeting where we also discussed international collaborations of this committee.

One of the things that became clear from reading that is that a lot of the barriers--actually it wasn't FDA and whatever the European thing was because there is increasing harmonization, but actually, OHRP, and whatever issues related to patient protection, et cetera.

I am just wondering, a lot of what Greg seemed to talk about here--I mean, we talked a little bit about getting an experimental agent. But it turns out that of all the things that we would think there would be a huge problem with, the Peginterferon. I mean, he said two companies or three companies no problem.

Maybe we have a meeting at the wrong place. I mean, maybe we should be where the Pope is or something like that, or maybe the Pope could help us out actually here, and try to work on something which is really the obstacle to doing this and you have suffered through this.

DR. REAMAN: The original hope was that there would be harmonization of regulatory guidances related to human subject protection. I think what we have done--and it was really the EURAMOS study and working with the NCI and

the NCI working with OHRP that allowed us to develop sort of an alternative pathway, if you would, with respect to who has to have a federal-wide assurance, and does it have to be every single institution that is participating in a study, and if they are individual institutions, the answer is yes,

But if they are recognized cooperative or collaborating groups outside of the United States, then only the coordinating center has to, and that has actually eliminated the problem.

So, rather than appeal to some higher authority, the very highest authority, I would rather leave well enough alone and just keep doing the work-around that seems to be working right now.

DR. LINK: But the work-around was basically that COG could not be the coordinating center. In other words--

DR. REAMAN: Or EURAMOS, COG could not be.

DR. LINK: Also, for the lymphoma studies.

DR. REAMAN: Actually, the coordinating center for the lymphoma study was more than just OHRP related as much as we would like to blame everything on them, I can't.

I think the EURAMOS study, we could not be the coordinating center and I am not sure if without all of the

institutions in Europe having federal-wide assurance numbers.

DR. LINK: Who is the higher authority, OHRP or the Pope?

DR. REAMAN: Guess.

DR. S. MURPHY: Greg, returning kind of to the topic of today's meeting, though, you are in a position where you have to strategically think about the impact of all these regulations and how are we going to work more collaboratively in a global way for new drugs.

Do you have any comments or from your perspective, you know, some ideas as to how we should try to capitalize on the fact that --

DR. REAMAN: I think there are some variables that need to be considered. I mean. what is the critical issue for doing international collaboration? The patient population size, the strategic opportunities, or the rapidity with which you want to do a trial, do you already have ongoing scientific collaboration. I think all of those things need to be part of the equation.

Then, the other big consideration is how do you collaborate internationally with a single institution or

with an established group and where there is an established group.

We have been successful in helping groups establish themselves. It is far easier, but where there are specific patient populations like children with adrenal cortical carcinoma or a large volume of children with retinoblastoma, both very rare diseases, then, in those situations you have to do single institution collaborations.

Did I answer your question?

DR. S. MURPHY: You showed that very well. But what I was getting at is we have these sort of parallel regulatory processes, and we would all like to think that we could facilitate some synergy, new agents to develop them--

DR. REAMAN: I think the process is in place for doing clinical trials. These are not all new drug trials although there are a couple of unapproved agents that are being studied. But I think the system is in place that would certainly permit us to do international Phase 2 studies.

Whether we do it on national Phase 1, I don't think there is the need for that as long as there is good communication. But I see no reason why we couldn't do Phase

2 studies internationally.

DR. LINK: In fact, in the transcript from the 2003 meeting, it was interesting that people felt that early phase studies would be easier to do environment than actually the big, randomized, Phase 3 studies that you have launched, because it takes fewer--you would really pick a few big institutions and do Phase 2's.

Go ahead, I am sorry, Ken.

DR. COHEN: Greg, I just had a question, which sort of gets to Sharon's comment a little bit, which is it seems to me that we have utilized the international outreach as a number issue largely. I haven't had, don't know of an experience where we have used it for a labeling indication or in this patient population.

Have we, in fact, ever done that? I mean. I know we do it because we need more retinoblastoma kids or adrenal cortical carcinoma kids and we need bigger numbers. We are going to do that in medullo probably, in infant medullo coming up.

Is there any experience actually dealing with this group and the European group in terms of a true, new drug and those regulatory hurdles in the concept of a labeling

indication>

DR. REAMAN: There isn't much experience with labeling or studies that go for labeling indications even with just COG alone. So, as far as the international studies, no. But I wouldn't imagine that it would be impossible at all.

DR. PAZDUR: We do it commonly in adult indications. I would say that there is almost an increasing norm that studies have an international focus rather than totally in the United States and, as Karen pointed out, sometimes completely outside of the United States with data quality that is very good.

Could I ask a question? Of the studies that you presented, how much of the actual accrual is coming outside of the United States?

DR. REAMAN: The EURAMOS study, half of it, but that's not a COG-coordinated study. I mean, it's a shared coordination.

The others are just starting to get the international accrual, but we don't expect it to be probably any more than 10 percent with the exception of retinoblastoma and adrenal cortical carcinoma.

DR. PAZDUR: That's a real problem. You know, when we are talking about international studies, it is a numbers game in a sense. The rapidity of accrual and what we see in adult diseases and adult indications is frequently the vast majority is coming outside of the United States, you know, with sites that you wouldn't even expect, Eastern Europe, India, South America, China, et cetera.

I am wondering if this is to be really effective, it has to be a significant accrual coming outside of the United States.

DR. REAMAN: We are just beginning this, so I mean this is all within the last two years.

DR. PAZDUR: Do you think the OHRP issue is the main issue?

DR. REAMAN: No, I don't think so. I mean, now that we have established an understanding of who has to be viewed as responsible, and what we can do with respect to federal funds as far as providing tangible assistance, NCI-supplied drug, supplying diagnostic review criteria assays that are involved in stratification or patient therapy considerations, I think OHRP is not a big issue at this point.

DR. LINK: Dr. Santana and I sit on a committee that actually Malcolm attended just a couple of weeks ago where a member of the committee is the chair of multi-country cooperative group in Western Europe for Phase 1/Phase 2 studies.

So, the collaboration, to get back to my comment this morning, the networking, the fact that in pediatric oncology, we know each other actually can be translated very easily to Phase 1/Phase 2 studies without very much difficulty or challenge other than some of the regulatory things.

So, it sort of can happen yesterday forget about tomorrow.

DR. WINICK: Without trying to sound too Pollyanna-like, I also think that the fact that you have now established international collaborative efforts tends to allow for additional because, for example, I can only speak to ALL, one of the difficulties in the Phase 3 trials, even if smaller groups of infants where there are particular difficulties is that the groups evolve with different backbones to their therapy.

So, it was hard to look at an experimental agent

when the backbone therapy was different. But now that there is some collaboration established, I think it will be easier to--it will be a primary goal now to make sure that there is the backbone that people can agree on so you can then assess the effect of new agents. So I think that you have started something.

DR. REAMAN: And when people actually realize that no backbone works, whether it is theirs or yours, I think it is much easier.

DR. LINK: Other questions for Dr. Reaman?

[No response.]

DR. LINK: We can continue now with our discussion, if there are other specific questions, Karen, that you would like us to address?

DR. WEISS: I am glad timing was this way because we did get back. I mean, we had some really good discussions, but the focus of the meeting was to just talk a little bit, free flowing, brainstorming about this whole idea of international efforts, so I would just like to hear people's thoughts.

One of the things this morning, I think Victor and some other people brought up and Agnes mentioned in her

presentation, the timing issue. Currently, we have in the U.S., more experience because we have had these regulations for so much longer. So we are sort of at different places. But, in many respects we are a little bit ahead, because we have sort of been there, done that with certain other products that Europe is now looking at in terms of clinical trials.

Sometimes, though, we are kind of at the same place. Jean gave the example with nasopharyngeal carcinoma where it is one trial we are all kind of talking about it right now at the same time, which is I think a real ideal situation.

But in the future as the EMEA has more experience and there are PIPs coming in earlier and earlier, and the question is sort of how can we--it is hard to know exactly what is going to happen, but it raises questions about how can we try to satisfy requirements for these incentives, whatever, both in U.S. and Europe, when we are all going to be at sort of--U.S. and Europe are going to be at different places, and the pharmaceutical industry is going to have different sort of demands on them in terms of what they have to come up with.

I would be sort of interested in what the committee, if they have any thoughts or maybe to even explore why Agnes is still here, some of the questions about how this might work out. I mean, the whole idea is we really want to move the field, you know, in terms of the quality, t he timeliness of the trials.

Anyway, getting back to that topic is something I think of great interest.

DR. LINK: But if they have to develop a PIP early on, doesn't it make their work easier in the United States? I mean, they ought to have something ready to roll, to give you, even if they don't give it to you until they know that the drug is a success, or do you think that they won't be using that same format?

DR. D. MURPHY: I think if we are all in agreement. Again we present a lot of differences but the majority of the time we are, and we do have the same controls and we do have the same endpoint. Then, the fact that they have already agreed to a plan, hopefully, they will have told us that, you know, they will tell us that, and then we are going to be making sure that the Division is aware of that,

So that the Division, if it has any problem with it, then, that is when we are going to get back with him. So it is still going to be the same amount of work. But what we are all hoping is that it is preemptive work, if you will, and not at the end of the process.

Right now we are in a huge mixed bag, you know. We have got many products that are further along, and they are getting them now later. But eventually it will switch.

DR. REAMAN: I am just wondering if we have to go before the regulatory agencies, I mean even before the FDA and the EMEA. I mean, most of the pharmaceutical companies are global in their strategic thinking and planning and is there at least--and I don't know, but maybe, Greg, you can address this--is there planning at the very early stages of drug development, not for a pediatric plan, of course, but would there be an opportunity to think that that kind of coordination could occur before there are pediatric investigational plans that develop?

CURT: I can tell you that most pharmaceutical companies are looking at strategies in India and in China because of both the sheer patient numbers, the specific pathologies that are there that might be amenable to

treatment with targeted agents and the rising standard of care.

So most companies are developing East Asia and China strategies, as well as in India, the incentives are different--I mean because those are the areas where there is likely to be more growth in the industry. But that was the question I was going to ask you, what would make you trip your wire to go to China where there are good institutions and a rising standard of care?

DR. REAMAN: Do I have to answer that?

DR. CURT: Hypothetical.

DR. PAZDUR: The only point I wanted to make is that remember these PIPs are being made right after Phase 1 study, so that they are quite tentative here.

Can you imagine trying to really develop a whole development plan of a drug after a Phase 1 study, when you really don't even know the activity of the drug and anything? Basically, you kind of know if that the dose of the drug.

So, really, even though they are made, they are so fluid here, and have some issues of changeability, you know, further communication that I am just wondering if we really

have to realize that, that these are really very, very tentative plans. They are written and that they could change at anytime here depending upon what the Phase 2 studies show or interest in other areas, competitor drugs, et cetera. There are so many factors that come into play here.

DR. COHEN: Has any PIP actually gone to closure? I know it's early. So has anybody actually written something and actually gone through the whole process and actually completed?

DR. BLANEY: I just have a practical question. Our legislature has been time limited. Is that true also because I would think that having to do a PIP at the end of Phase 1 for industry is quite burdensome and that you are surely, if you haven't already, going to have a back lash to having to develop and redevelop these kind of plans. So is this a permanent legislation, or is it time limited?

DR. SAINT-RAYMOND: No, no, it's permanent. There will be a review at 6 and 10 years. It took us 7 years to get it, so we have to plan for a longer timeline to revise it potentially.

But that is a point that is I would say a sore

point for industry clearly. I hear a good reason for maybe coming later but, again, think, a number of products are only for children, vaccines are only for children, most of them, and these products we would never see, which also doesn't make sense.

So, there are reasons why it may not be possible to have a PIP early, and the legislation allows for exceptions. But the rule should be to start planning early. Again, it doesn't mean that everything has to be done or all the details have to be come up with, but it is changing the way industry is integrating the pediatric development.

DR. ADAMSON: One of the differences between a PIP and a written request is that once the written request is issued, it is done. I mean, that is the written request, and to try to go back on that is a major challenge. Correct me if that is true or not true.

DR. WEISS: There are and Victor did a nice presentation back in June. Most of the written requests actually there are requests that are made to the FDA to modify it. Most of the time it is just to extend the timeline.

But there are some times, too, when they actually

change an indication. I think it was imatinib. It was based on some adult, that there was a written request early on, because of its activity in the CML and the relevance to pediatrics, and it was going to be I think in like relapse, and then based on the data --

DR. SANTANA: [Off mike.]

DR. WEISS: Right, so it was changed based on ongoing accruing data in adults and other ongoing information so it was more streamlined and more appropriately modified. So that can be done.

But it is a legal contract, legally binding, and so unless there is specific explicit permission granted from FDA to accept those changes, they have to follow that plan.

DR. D. MURPHY: They have to have amendments; in other words, normally, what they would do is call the Division say, well, we think this has happened, we want to change the protocol and the Division would say yeah. That doesn't work, okay, but they have to call and then get an official rewritten written request. But I would say to you that it is unusual for a written request to come to the board, exclusivity board, that doesn't have amendments to it, unusual

DR. ADAMSON: What I was going to say, if you take the sphere of PIPs and the sphere of working requests, because they are happening at different times, there is clearly going to be overlap that you can predict before you ever go into the clinic, and it will come back to why not develop a very clear guidance.

Before you go in the clinic, you know what you are going to want, and say these in general are--and I know you have some of this--but align them, the Phase 1 requirements, the exposure requirements for different age buckets, the potential Phase 2 design that we look at, so then at least industry says, okay, we know we have to go on with our PIP now, but if we go on with this PIP, we know it's going to actually meet some of our written requests when the time comes to go for that written request.

DR. SANTANA: I wanted to get back to Greg, if you could kind of give us an indication. Historically, sponsors, pediatric plans don't come into the radar screen early on, no offense to any sponsor in the room, but that is the reality.

So, now this process in Europe is going to force you to at least think it earlier on. So what conversation

is Pharma having about this? What are your internal discussions?

DR. CURT: I think if your concerns are that industry is not going to pursue pediatric oncology trials, they will, because the incentives are there, and they worked, and they will continue to work.

I think we certainly preferred the FDA's focus in Phase I on safety and pharmacology. There is going to be a commitment in the U.S. to go to pediatric studies early. These discussions begin normally at the end of Phase 1 and when you are considering Phase 2 studies. So they do occur early.

The differences I think in the U.S., you plan your pediatric strategy based on what you are learning in the clinic and to articulate a Phase 3 strategy at the end of Phase 1 is more difficult. But given the incentives that are there, pediatric trials in oncology will be done and we will deal with whatever the regulations are. I mean, that is something--we are a highly regulated industry, and we will do that.

The only disadvantage potentially is that because, in one portfolio of studies, you are thinking about a Phase

3 strategy based on efficacy and, in other portfolio of studies, you are looking at safety and pharmacology and thinking how to do Phase 2 studies or late Phase 1, early Phase 2 studies in pediatrics, that it makes it more difficult to launch global studies with the same patient eligibility requirements and primary and secondary endpoints.

DR. SANTANA: Please correct me anybody at the table, but it was my impression that the early focus of the pediatric oncology written requests were truly on safety and PK. But there has been an evolution among the oncology group that efficacy is now coming to the table and those studies are also being requested in the written requests that are being issued now.

So, there has been an evolution. I didn't hear you say that the agency only focuses on safety in the Phase 1 component.

DR. CURT: No, end of Phase 1 and then in the Phase 2, you try to make informed decisions about efficacy based on what you have learned to date in the clinic.

DR. DAGHER: Ramzi Dagher, Division of Drug Oncology Products. As was mentioned before, because of the

legislation and the regulatory history, when it comes to the drugs, we have a fair amount of experience with the incentive program, the BPCA, under which all this occurs.

So, you are right that early on, the focus was mainly on the PK and tolerability issues. We have moved a little bit but still, as was discussed today, there are a lot of disease areas where whether it is in a PIP or even in the written request program where you might have more data when you get into that than you might across the ocean.

Still, it would be very hard to justify in many disease areas, even in this country, specifying one or more randomized Phase 3 trials in a pediatric oncology setting when you still don't know whether the drug has even have activity in one or more pediatric settings.

So, that is still a struggle for us right now and, although we have moved, it is still a struggle. Now, in the area of solid tumors, this is much more difficult than in the hematology malignancies for a couple of reasons.

One, in the hematologic malignancies there are some situations where even though the diseases aren't identical as those that we see in the adults or the young adults there, similarities in biology and sometimes in

epidemiology and, in the experience with a specific drug, that actually allow us, using the Phase 2 data sometimes, to make decisions about not just extrapolation but, actually based on the pediatric Phase 2 data, make decisions about efficacy.

So, whether it was clofarabine or even imatinib--you know, people forget. Imatinib has specific pediatric indications, not just the ones that were talked about earlier, but even the leukemia indications based on pediatric-specific data from the Phase 2.

So, let's not knock the Phase 2 data all the time, the Phase 2 data in some settings can be evidence not just for activity, but also of efficacy. The place where I think this is most challenging is really in the solid tumors.

DR. PAZDUR: If I could go back to the meeting that Jerry mentioned when everybody was in the room about 10 years ago, one has to remember how this whole pediatric plan came about of developing drugs. Remember there was really a dearth of activity in pediatric oncology drug development like virtually no written requests were being written, you know, there was a problem here.

What we talked about with Mac even before we went

into the meeting, Jerry, was the issue of how to do this in a logical fashion that would make sense. First of all, it is a very high risk area and how to reward people for--and sponsors--for developing drugs. So, yes, you can do a Phase 1 study and just if it can't go any further because of the toxicity, we will give you exclusivity.

Do a series of Phase 2 trials. For that effort we will give you exclusivity. It really was an effort here to really promote labeling and drug development in pediatrics, because there really was no activity in this whole area here. So, we have been successful and with success sometimes you start looking at, well, how can we improve the program.

But I don't think we are mandating at this time and saying you must do a Phase 3 study unless it is warranted. Nobody wants to do a Phase--you won't do the Phase 3 study, you know.

DR. SMITH: Questions both to Europe and the U.S. in terms of what are your expectations in terms of rationale for why this particular agent from this particular sponsor warrants evaluation in a particular population and, therefore, whatever benefits would accrue to the sponsor?

DR. SAINT-RAYMOND: It is a difficult question because you could say we need all this information before we make an informed choice and, certainly, that is the best scientific approach.

We have seen companies come in, when they didn't need to have a development plan in children, they also are interested because there is an incentive and they are also coming a little bit like it's a written request, propose a completely different indication.

So, we have also information from the company, and we discuss with them, say where do you see there would be-- as I said before, it is planned for this plan to be revised and, clearly, at a certain point, we may be too over-ambitious,

We also learned with experience how we can make them better. We are just starting so give us a little bit of time to learn from our experience. But the rule also applies across therapeutic areas, was not made for oncology. Maybe oncology again is a little bit outside of the product of developing drugs.

In other areas, the issue is reasonably simple, and it is not as difficult as this one. At the same time,

we believe that there is a possibility to gain some development that we had never seen before.

DR. D. MURPHY: I am going to ask the experts to answer most of this question, but I just want to point out that as far as our criteria all along, have been trying to gauge the need, as long as there is a need--in this area, I just find it hard to think of when we would say, no, we don't need any more products.

I mean, again the only question would be prioritization of products actually and that would be something that we would have to get from the Division and, sometimes, we have actually taken this issue to commit public committees to discuss outside of oncology.

We had this in HIV, you know, how many more products for neonatal transmission do we need, should we keep doing this, you know, because again it was a diminishing population in certain areas, you know, that sort of issue.

So, as of right now, just to make sure everybody is aware, the agency has issued over 40 written requests for products for oncology and 27 of those have been in solid tumors, refractory tumors, relapsed.

I know Victor went over a lot of this recently for you all, but we know there have been at least 9 that were labeled and we have additional ones we think have been submitted. I think that that is encouraging but, clearly, I guess what I would turn the question back to you, Malcolm, is do you think that actually, we are anywhere near the point where we would say, gee, we don't think we have a need for any of these?

DR. SMITH: No, but I would be very careful to distinguish need from probability of success. We certainly have populations that have need, but, you know, neuroblastoma, high risk. We have plenty of need, but we have 20 different drugs that we might study, 20 different classes, 20 different targets, what kind of information would help us learn prospectively, the information that is going to help us make the true decisions about prioritization.

DR. PAZDUR: Malcolm, drug companies grapple with this problem every day of how to take their development plan and one of it is risk reduction, risk reduction, risk reduction and it's a stepwise approach.

First of all, and this is why we devised the

pediatric plan in the way we did, to do a Phase 1 study, obviously taking and looking at the totality of evidence, what is the activity that we are seeing in adult tumors, if this drug is active in lymphomas and in leukemia, as well, one doesn't have to be a rocket scientist to figure out that that might be an area that you want to take this in pediatric malignancies.

If it is a novel mechanism of action, yeah, it has a lot more interest and especially if you know, for example, a particular defect that it could be married with within the tumor, for example, the ecchyluzimab [ph] issue with PNH or imatinib in CML, that type of situation.

So, it is really a stepwise approach. And there is not one answer here. But it is something that industry grapples with every single day of which drug to take from a Phase 1 to a Phase 2, if you see activity in a particular malignancy in Phase 2, you take it in that direction. So, it is not an easy question to answer.

DR. SMITH: It's not easy. But industry does grapple with it and so I guess a question is how can we best grapple with it because we are the pediatric research community that is trying to find the best ways to make these

prioritizations.

DR. PAZDUR: But here again, what information do you have at the time that you are making the decision both from adult tumors, the evidence of preliminary activity, the mechanistic activity, animal model activity. It is a compilation of data here, it is not just one thing and it's a problem that is paramount in the whole oncology drug development picture, not only to pediatric drug development.

Obviously, there are specific issues here because of the limited population. But, even in adult tumors, this is a major dilemma of how to develop these drug unless one really know a mechanistic approach of the disease and the drug.

DR. SMITH: I know Greg has been waiting, but so the preclinical in vivo data, you know, that is one source of data. But there are many other sources. So I would agree with that, but to bring, you know, to have some formal process or standards for what you are going to expect for the different types of data that can be brought to the table to justify why this should go forth.

DR. CURT: I am going to say something that I know you all know, but I think I have to put it on the table, and

that is that one of the other things that is culturally different about medical oncology is that many, in some cases, not most of the physicians who are making these decisions in industry are pediatric oncologists, and they are not only schooled in the art and the science of clinical trials.

But they also are very familiar with the unmet medical needs of kids with cancer so there is a real opportunity I think for a partnership between industry and the pediatric community because a lot of your contraires are in industry.

DR. WEISS: We asked Dr. Blaney if she could be the honorary acting chair because a number of people have to leave and we were scheduled to go a little bit longer and, as long as people have the time and can stay, we would love to sort of hear your thoughts.

Whoever can stay a little longer and continue this discussion, that would just be wonderful. So, I wanted to make that announcement.

DR. D. MURPHY: I guess one of the other things I l would like to say is we keep talking about the differences as something we have to somehow fix. I think actually the

timing differences--and I am truly not saying this as Pollyanna as you said--are truly opportunities particularly in this arena where very early, you are particularly not going to have a lot of information.

They are going to be. They are going to be developing the PIP, and we are going to be at Phase 2, you know, 3, we are going to be developing our protocols. And we will be talking to them. Then that will be an opportunity for them to learn from us, and for us to learn from what has been going on with them, to change these.

I really do believe that it gets to your question, Peter, these are documents that are amenable to change over time and we are hoping to be informing each other and all of these issues of, well, what do you learn.

It may be that what they are learning early on would be informing, by the time we get to our part of it, that would change very much how we are going to approach it.

DR. REAMAN: I would like to also be Pollyannish about this, and I think there is an opportunity for being different and being at different time points because neither system is likely to be perfect. So, if both evolved, then, maybe that evolved system will be the best.

But I guess my concern about being at different time points and requiring different information and planning, how that is going to potentially impact on what might be a trial development, I mean, how an early requirement with a PIP might actually require a study to be developed, maybe not the best study that could be developed because not all the information is available. Then to me that's the real lost opportunity, not the lost financial opportunity, the lost time opportunity, but the real lost opportunity for evaluating a new agent.

DR. SAINT-RAYMOND: I see your point and maybe with time we will learn to ask for less at the beginning or nothing and maybe later on some data when we have a better process to select the product.

At the same time I see those as an opportunity for companies maybe to integrate better nonclinical development before they go to Phase 1 in children or Phase 2 in children and seeing that there will be an obligation for them to go for some development maybe accumulating better animal models whatever is needed, not just going to Phase 3 immediately without knowing. That is not what we are asking for, but we ask them to really build on the data and build on the

knowledge to make sure that we will make the informed choice later on.

As I said, we are at the beginning so it's too early to say how we are actually working. But that is the idea. We are testing the system also ourself to see how we can get to the best decision.

My view is that companies will have also an opportunity to go to the FDA after having maybe the first draft of the PIP and saying, well, that is what they have asked us, it's crazy Europeans, for the first time, look at the data to see if you can make something out of it, or maybe it's completely crazy possibly.

But I think we can learn on both sides. Maybe you will start earlier, we will start later, and we will get to something more compatible.

DR. WEISS: I was just going to say that, you know, to some extent this issue, too, about the timing and going forward certainly with the written requests when you don't have the full data, it is something that happens now. I mean, I can think of a couple of examples, irinotecan and the rhabdomyosarcoma and temazolimide [ph], where we have information on label now based on written request and

exclusivity for information that is in the label now that doesn't really have any bearing on reality now of how those drugs are used.

I look at that and say, gee, I wish we knew then what we know now so that we could have actually worked to design better studies that had more informative--I mean, the field is actually using these drugs and they are more useful now than what the labeling would tell you because of the time of when we did the studies.

So, you know, in the ideal world, you know, if Europe was coming along with those drugs now, we could say, hey, what we learned, you know, this is what we learned, and not just FDA, of course, but the whole pediatric community, let's take that information now and design better studies that Europe can have that will benefit everybody.

I mean, this is just the situations that already are occurring.

DR. CURT: I think this is a very healthy and useful discussion. As someone once said, in God we trust, everybody else provide data. Maybe the thing to do is to actually plan a prospective analysis at some point downstream of what has worked in one system and what has

worked in the other system and actually decide now what you would need to be able to get those metrics, and then make a very rational decision on how to hybridize or change the process in pediatrics.

DR. SANTANA: I want to follow up. I think Dianne was heading in a direction that I want to follow up. I hope we don't leave the session saying that everything has to be the same because there may be real opportunities to ask different questions because, once they get exclusivity, you are done, you don't have any more opportunity to go back and work with the sponsor on exploring a new idea or a new requirement.

I hope that both agencies view this when there is the opportunity to do it together, because of efficiency of time and resources, great. But there may be other opportunities in which diversification is really what we want, and we want both groups to ask different questions because we are going to benefit more in terms of having other populations that we can get information from.

So, I think both sides are right. But I think a lot of the discussion today has been kind of bringing things to the same point. And I think we need to remind ourselves

that there may be points where you diverge, and that is healthy, too. It is just a matter of resources and those kind of things that have to put in the equation, too.

DR. SCHWARTZ: Listening to this, I am going back to what you said there. We really don't know what it is going to be. It could be they are having two different pathways give benefit because we are looking at different times of various things. But it could also turn out that there are real glitches in that and it probably will be a mixture of one and the other.

The interesting thing I thought was what you mentioned--was what do we want from us right now. Is it that we should have a committee that is looking at how it goes so that maybe in five years or six years, or whatever the different rules are, that we start to harmonize it, or do we also need committees doing things like what Sharon said--so that we are evaluating things like response-based things or biologic markers or whatever surrogate measures we can use so that both groups can bring them in because I think we need to be kind of monitoring and working with--it sounds like you are doing a lot of liaison behind the scenes, you know, talking with your colleagues and coming up

with good plans, which is probably what is going to make this work. But I wonder is that something that needs to be formalized under different things specifically.

DR. D. MURPHY: Again, not being my field, I would hope that is what you do all the time in a way, that you would be looking at what is working, what is not working. My assumption would be that is what is going on--because I can tell you not from Europe versus U.S., but so many of these trials are done both places, and what we are trying to bring in people--and Victor knows this--to look at trials that have failed, and trials that we are having difficulties to define better trials.

Now, that is not addressing whether it is Europe or U.S., it is just how do we do a better trial. You have such a unique situation here and an opportunity to have your hands around most of those trials and be able to do that, that I would hope that that would occur because we can only bring in so many people to do so many categories of trials, and you all seem situated to do that for ped oncology.

DR. S. MURPHY: I would like to return to a point made earlier by Dr. Mathis about how, in the U.S. FDA, these laws are going to expire again in 2012, and the clock is

ticking here. So my question to the FDA staff in this pediatric realm in oncology, let's bring it down to that, what are you shooting for? What do you think would be the evidence that you would have to put forth or that we would have to help you gather to say that this has been a great success and should be renewed and made permanent or something.

Have you talked amongst yourselves and identified parameters that you think will be a success? What is success? How are we defining that?

DR. WEISS: Let me ask Dianne just because they have been through this now many times as BPCA has been renewed, reauthorized every five years. I think it is written in that it sunsets every five years, and they have to prepare a humongous report to Congress. Elaine may know some of this, as well.

Congress looks at that and makes determinations obviously based on our input and recommendations about whether it should be reauthorized and, just by the simple fact that it has been reauthorized many, many times, I think the widespread view is that people do believe that it is a success.

Dianne, if you can just comment on sort of the metrics used.

DR. D. MURPHY: The metrics, in the new legislation, they have lots of things they want us to look at, what types of requests, what kind of studies. There are lots of what kind of labeling. But, when this all began, we knew we had to renew it. We asked ourselves how to do that.

So, we had to put in place some tracking systems because they are not tracked in the usual regulatory way. One of our first metrics was did the product get studied, you know. Well, first of all, did we actually get something issued or get something studied in this area either in the written text or the PREA. So, that was one thing. Did we get some studies requested, then did we get the studies, and what did the studies provide us.

We have been trying to--and we have actually published a couple papers on this, and we are trying to get more information out there, and what we have learned so far, which is are there new safety signals, what did we learn about dosing, what did we learn about--we have half of the hypertension trials not working. Why in the world is that? We understand that, we think. So what is going on?

We have had people come in and look at that and we are having a paper coming out on that, and it has to do with how you do the dosing and how you do the endpoints.

Actually, something interesting with diastolic, you know, which when we sent to one journal, which had a number of people say, well, no, no, diastolic can't be the answer because systolic is predictive of the mortality for adults.

I think we are learning a lot is the answer, is what are we learning from this, and is it useful, and is it helping us provide therapies that are dosed properly, that people know how to balance whether they should be using them because they understand the safety profile and whether, if they are not working, why are they not working, and is it something to do with the way children respond differently, or is it something to do with the way we are measuring the endpoint.

So, our metric is how much work are we getting done, how much knowledge are we getting from that work. Certainly I think for oncology, it is the same metric, it is what trials are we getting and what are we learning from it.

I don't know if you guys have anything else.

DR. PAZDUR: Sharon, I am taking you to task. It is not what the FDA and how it defines success. It is how you define success because, ultimately, you guys are the end users of the product that ultimately how the patient defines success. That is the real importance of this program.

So, how do you define it? It could be like Peter said, we haven't made improvements in overall survival for many years. Should we be measuring it by the survival rate? Should we be measuring it by the number of new agents that are coming in to pediatric clinical trials? How do you define success?

Ultimately, it is obviously the most important one, the survival issue. But there are many penultimate steps here before you get the ultimate step. But it ultimately is what you want. It is not what we want.

I think that it is very important for people to take away, and I am turning the meeting over to you to end this meeting, is how do you define success of the program.

So, Sharon, do you want to tell us?

DR. S. MURPHY: Thank you for the opportunity. I certainly agree with you that it is up to the community, patients, advocates, scientists, physicians, industry, and

all of us to agree on what are the parameters of success and it may differ depending on your perspective obviously.

I just wanted to hear the agency response, that's all, and so I got a wham, you know.

DR. PAZDUR: I didn't mean to wham you. I just wanted to put the real importance of it is really how the community defines the success.

DR. D. MURPHY: If we ended up with a bunch of trials that were not informative to physicians on how to better provide therapy to kids, these programs wouldn't be renewed. But we can tell you that overall we are finding in a round number, about a fourth of the time we either didn't have the dose right, we found a new safety signal, or it didn't work.

Well, think about an adult and all the medicines they took if we just said oh, well, a fourth of the time we don't know what we are doing with your medications. So, we think that, in itself, has been a powerful metric to say, yeah, we need to keep looking.

The other statement, why would ignorance be good public policy? It has just never struck me that that would be a good thing to do for children.

DR. SMITH: So, Rick, the challenge of defining success. It is more than just how many trials, Phase I, trials you did. You could get a lot of Phase 1 trials and that is not going to help much. One metric would be have we identified two agents a year, three agents a year, that are actually active.

We may study 10--and you know well that we have had a lot of negative Phase 2 trials, they are good information. It is nice to be able to use the best information we have to say, I think, based on what I know, this might work in this disease, take it in, and increase our hit rate, so that we have two or three active new drugs in some of the cancers that are so hard to treat now.

DR. ADAMSON: I think if you look at the impact across pediatrics, the programs have been a resounding success. They are not perfect programs by any means and there is always room for improvement, but there has been a dramatic success.

In oncology, I think the challenges are not identical and therefore I would personally classify it as a modest success, but it depends on what level. So, at one level, a very basic level, is companies call me, companies

call Susan, companies call us, we call them, and it is not as though you are on hold with music, and then there is a message and no return call.

So, even at a very fundamental level, it has improved communication, it has opened the dialogue at a point in time that is very different today than it was 10 years ago. So, yes, there are I think metrics that are easier to come by, but the impact has been felt and we have to put our full weight and our full support to making sure that this does not sunset in 2012.

We can always improve it, but the impact is there. And we have to assure it, not just for pediatric oncology, but for all the pediatric specialties.

MS. VINING: I think one of the questions I would like to ask this group is to think of it a little differently, if it did go away, what would the impact be, because we are fighting to keep this around and we really applaud the EU for making it permanent. It was something we tried very hard to get for PREA to be permanent and we will have to take another bite at that apple.

In part it was politics that caused the two of them to be married, two being BPCA and PREA. That is why it

is coming back again in five years. I think if we can get this PREA permanent, that is something that will be a playing field that we can improve upon, like the EU is going to do, where we know it will always be there and we can go back and take a look at it, and modify it and improve it, and change things that have to be improved, b

But the story that we need to think about is where we are now 10 years down the road is so far from where we were 10 years ago, what do we have to tell Congress.

I think you, as scientists, would have to say we can't go back. If we go back, this is what is going to happen to kids, and while we wish that we could improve farther than where we are, where we are is so far superior to where we were, that is the story that has to be told I think.

DR. WINICK: I think, given the relatively short time frame--I mean every five years by the data that have been presented here--is very short in pediatric oncology time span. The other way to approach an endpoint would be how many new--not new agents have been introduced, but new classes, because one of the things we struggle with is the notion that we have to get beyond standard cytotoxic therapy

and, to me, it is far more complex to evaluate some of the biologic agents than it is a standard cytotoxic agent where you have an MTD and DLT and things that we all are comfortable defining.

It would be nice to see how many new, truly new pathways or venues or classes are facilitated by this process.

DR. REAMAN: I am just going to go back to Dianne's comment about ignorance can't be good for children. I would have to say that I think having been involved with this 10 years ago, there has been very, very dramatic success. I mean, we couldn't get access to new agents with the NCI's help until a drug was already approved for an adult indication, so not after the Phase 1 studies, not after the Phase 2 studies, but after approval, and sometimes long after approval. So there has been a very real impact.

I think measuring the success isn't going to only involve what you, the FDA, or what you, EMEA, do, but what we do also because we can't keep doing the same kinds of trials that we have done for the last 15 to 20 years.

We can't take 5 years to ask a question and answer a question when sometimes there are two or three or four

questions that are actually involved in these clinical trials.

We are as much at fault, if you will, for not realizing the success. I don't think we can just keep pointing the finger but we have to start doing things very, very differently also.

DR. WEISS: I just want to thank everybody for their discussion. This has been remarkable. I sort of worried since I didn't have questions to stimulate discussion that maybe there would be long periods of awkward silence. But definitely you are not shy and there has been a lot of excellent discussion.

I look upon this as maybe the start of some additional discussions particularly as Europe bets more experience under its belt, maybe we could have some further areas to explore on how to improve things.

Thank you very much and have a good trip back and hope you avoid the traffic jams.

[Meeting concluded at 3:29 p.m.]