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CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE

OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. LINK: Good morning. This is a meeting of the Pediatric Oncology Subcommittee. As I think you know, we are here to discuss endpoints for trials intended to support the approval of new drugs for the treatment of pediatric brain tumors.

Before we start, I would like to go around the room, so we can have the panelists introduce themselves. Why don't we start with Dr. Pollack over there in the corner and go just around the room. Tell us your name, your affiliation and your area of expertise.

Introduction of Committee

DR. POLLACK: My name is Ian Pollack. I am a neurosurgeon. I am from the Children's Hospital of Pittsburgh.

DR. ARMSTRONG: I am Danny Armstrong. I am a pediatric psychologist. I am at the University of Miami.

MR. LUSTIG: I am Craig Lustig. I am the Executive Director of the Children's Cause for

Cancer Advocacy and a pediatric brain tumor survivor.

DR. SWISHER: I am Luice Swisher. I am a new Patient Representative here. My daughter had medulloblastoma seven years, and I have been involved in advocacy since then.

DR. BOYETT: James Boyett, biostatistician, Chair of Biostatistics, St. Jude Children's Research Hospital.

DR. REYNOLDS: Pat Reynolds, Director of Developmental Therapeutics at Children's Hospital of Los Angeles, University of Southern California.

DR. GOLDMAN: Stu Goldman at Children's Memorial. I am a pediatric oncologist.

DR. WARREN: I am Kathy Warren. I am a pediatric neuro-oncologist at the National Cancer Institute.

DR. COHEN: I am Ken Cohen. I am a pediatric neuro-oncologist at Johns Hopkins.

DR. BLANEY: I am Susan Blaney. I am a pediatric oncologist, Texas Children's Cancer

Center.

DR. KUN: Larry Kun, radiologist-oncologist, St. Jude Children's Research Hospital and Pediatric Brain Tumor Consortium.

DR. MEYERS: Christina Meyers, Neuropsychology, at M.D. Anderson Cancer Center.

MS. CLIFFORD: Johanna Clifford, Executive Secretary to the ODAC, FDA.

DR. LINK: I am Michael Link, a pediatric oncologist from Stanford.

DR. PACKER: Roger Packer, pediatric neurologist, Children's National Medical Center, Washington, D.C.

DR. SMITH: Malcolm Smith, pediatric oncologist at the Cancer Therapy Evaluation Program at the National Cancer Institute.

MS. HAYLOCK: Pamela Haylock, oncology nurse and Consumer Representative.

DR. GOOTENBERG: Joe Gootenberg. I am with the Office of Oncology Drug Products, Division of Biological Oncology Products in the FDA. I am a

pediatric oncologist.

DR. SRIDHARA: I am Rajeshwari Sridhara, Statistical Team Leader, Oncology Drug Products.

DR. DAGHER: I am Ramzi Dagher from the Division of Drug Oncology Products, FDA, and pediatric oncologist.

DR. WEISS: I am Karen Weiss, also a pediatric oncologist. I am the Deputy Office Director, Office of Oncology Drug Products, FDA.

DR. PAZDUR: Richard Pazdur, Office Director.

DR. LINK: Let me go through a couple of administrative things. First and foremost, as we have learned from the microphones, to make them work, you push the button, and the transcriptionist would like very much for us to use the microphones. You know that they are on when the little red light goes on, so if your thing isn't working, try to find one that does. The second thing, when you are finished talking, turn them off.

If you have something to say, try to get my attention, raise your hand, something like that,

so I will put you on a list here of people that want to make some comment.

Another point, please turn off your cell phones. They are very annoying.

What else can I tell you now?

Let me introduce Johanna, so she can go through the Conflict of Interest Statement.

Conflict of Interest Statement

MS. CLIFFORD: Thank you. The Food and Drug Administration is convening today's meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

The Pediatric Subcommittee will discuss endpoints for clinical trials intended to support the approval of new drugs to treat pediatric brain tumors. This topic is a particular matter of general applicability.

Unlike issues in which a particular firm's product is discussed, the topic of today's meeting may affect all products under development, as well

as those currently being used to treat pediatric brain tumors and their sponsors.

The members and consultants have been screened for potential financial conflicts of interest with respect to the products and firms that could be affected by today's discussion.

Based on the agenda for today's meeting and all financial interests reported by the members and consultants, no conflict of interest waivers have been issued in connection with this meeting.

We would like to remind the members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

In the interest of fairness, FDA encourages all other participants to advise the Subcommittee of financial relationships that they may have with any firm whose product they wish to comment upon.

Thank you.

DR. LINK: Let me go briefly through what is the plan for the day. As you can see from the agenda, or if you have it in front of you, we have the morning filled with presentations to help us come to some conclusions about potential endpoints to be used, and then after the break this morning, we will have time for questions.

What I would like to do is if there are burning issues that relate specifically to an individual presentation, we could handle them at that point, but I would like to sort of handle more general questions regarding all the presentations after all of the morning's presentations have been completed. After lunch, we will address the questions which you should have received, the meeting questions, which we are here to provide advice to the FDA.

If there is no other commentary, let me begin by introducing or asking Dr. Karen Weiss to begin today's session.

Opening Remarks

DR. WEISS: Good morning. First of all, I want to welcome members of ODAC and consultants to the Pediatric Subcommittee to ODAC. I very much appreciate your time that you devoted to preparing for this meeting, for being here today to help advise the FDA on this important topic.

As you all know, the topic for today is a focus on drug development for the treatment of pediatric patients with primary brain tumors, and in particular, we are going to focus on issues related to endpoints.

[Slide.]

As I said, the topic for today is to discuss pediatric brain tumors. But before we can talk about issues in pediatric brain tumors, we have to step back a minute and think about how that fits into the context of drug development and particular issues for pediatric oncology, because, of course, pediatric brain tumor patients are a subset of the larger patients, the pediatric oncology patients.

[Slide.]

But before we can actually talk about pediatric oncology, we need to then sort of think about some basics, and those are the issues that affect general pediatrics, because there are some very important pieces of legislation that are designed to help promote and develop drugs for pediatric diseases in general and those certainly impact on pediatric oncology as well as pediatric brain tumors.

In addition, we also need to think about some of the issues that are relevant in general oncology, in particular endpoint-related issues. So, if you think about my people or pediatric pyramid here, we are going to first, because I consider myself a pediatrician first, talk about issues related to general pediatrics.

[Slide.]

There are some unique things related to drug development in general pediatrics that really aren't necessarily applicable to the adult drug development world, and that is that there are really two main pathways for drug development and

to get data in pediatrics.

One is that there is a drug that has been intended and developed to study a unique pediatric disease. In that setting, the drug development paradigm is what everybody knows there are Phase I, II, III, etcetera, studies primarily done in the intended population, and then the indication and approval is for that particular pediatric use.

There is also a much more common situation that everybody in pediatrics is very painfully aware of and for which legislation over the past decade or two has been designed to try to fix that problem, and that is that there is a drug under study or approved for a disease that occurs in the adult population.

Again, as everybody in pediatrics is painfully aware, those drugs then tend not to be evaluated particularly in the pediatric populations. They just get used, primarily used as we say "off label," and there really aren't good data to really support the dosing or even the efficacy in those populations.

So, as it attempts to try to get and promote more pediatric data, there are two important pieces of legislation and. even though the focus of today's meeting is not to discuss these pieces of legislation, it is important to know about these, because they really do play a part and, in particular, the latter one, the Best Pharmaceuticals for Children's Act, or BPCA.

But BPCA and PREA, or the Pediatric Research Equity Act, are two important pieces of legislation that are really aimed at and developed to encourage or require, as the case may be, pediatric studies and pediatric data.

[Slide.]

Since a lot of people have questions about what these two are, on this slide I have just put down some of the differences in issues with them.

BPCA is commonly referred to as the carrot, and PREA as the stick. The reason why is that BPCA process, to get pediatric data, pediatric studies under BPCA, this is voluntary.

Companies can agree to do this or decide

not to do these studies, and there are incentives that are attached to developing and conducting studies as part of BPCA, and that incentive is six months of marketing exclusivity attached to the existing patent protection or exclusivity, while PREA, on the other hand, is required, and there are no financial incentives associated with that.

The other important issue that I have highlighted in yellow is that, under BPCA, the exclusivity is attached to the entire moiety, and that means there are many drugs that exist in creams and topicals and powders, long acting and extended release, and all that kind of thing, and, if a company does a study on one formulation, if you will, of that drug, the entire gamut of formulations and preparations receive the exclusivity.

In addition, for BPCA, the studies can be done for the same indication as used and approved in adults, or it can be for an entirely completely different indication, and, since Dr. Reynolds is here, I will mention one of them that I know is

near and dear to him which is Accutane or isotretinoins, which are approved for acne. There is a lot of interest in evaluating and looking at this drug for neuroblastoma. It would be a completely different indication.

Another example is tamoxifen approved and widely used for treatment, hormonal treatment in breast cancer. Under BPCA, this drug was studied and evaluated in children with McCune Albright syndrome, a completely different condition.

Under PREA, it is only the actual preparation or formulation of the drug, not all preparations, not extended release and other forms of the drug, and it can only be applied to the indication that is approved for the adult use. So, it has to basically be the same condition in adults as in children to be appropriate for PREA.

I think those are the main issues. As Dr. Link said, if there are any questions about this, we can discuss this later on in the discussion section.

[Slide.]

So, with that in mind, there are a number of challenges to pediatric drug development as a general concept, not focusing on pediatric oncology in particular.

That is, when you have adult data in an adult indication, whether it is the same or different than in children, the particular pieces of legislation basically say that it may be appropriate to extrapolate some of the adult safety or even efficacy data to children. But that is a very, very difficult thing to do.

It is much easier said than done, and the reason why is that there may be significant differences in the pathophysiology of the disease despite it being considered "the same disease" in adults and children.

Sepsis is one case in point. Lots of discussion about whether or not pediatric sepsis is the same as sepsis in adults, and we had lots of discussion when we were thinking about this particular scenario, because differences in outcomes, differences in the source of the sepsis,

et cetera, might make it very difficult to generalize data from adults.

The drug itself may actually work differently in the pediatric populations. We know that there might be significant differences in the pharmacokinetics particularly because of differences in organ maturation, and that is particularly true when you think about the very youngest of the pediatric age groups.

Outcome measures may be quite different and we have people here that are experts in issues about patient reported outcomes. It may be very, very difficult to apply certain scales that are appropriate for adults down to the pediatric age ranges to look at these outcomes, or drugs that are approved based on pulmonary function testing where it is very difficult, if not impossible, to evaluate PFTs in young children.

There are certainly differences across all the pediatric age groups when you think about neonates and infants all the way up to adolescents, and so therefore it may be difficult to even

generalize from one age group down to another. It may be very important to include all the relevant age groups in the clinical studies.

As everybody knows, procedures in sampling may be quite a bit more difficult in the pediatric populations. It may be difficult to evaluate pharmacokinetics fully because of the requirement for certain blood volumes or for various types of procedures.

Formulations, and this is a particular issue when you think about both PREA and BPCA, if something is approved in an oral tablet formulation, obviously, young children can't swallow pills, and the ability to develop an appropriate suitable pediatric formulation might be quite difficult.

Ethical considerations, not as much of an issue in pediatric oncology as it is in other scenarios, but the whole issue of putting children on trials and the fact that they can't legally give consent leads to a whole host of additional protections afforded for children.

Then, in many diseases in pediatrics, particularly pediatric oncology in particular and particularly in pediatric brain tumors, sample size considerations may make it quite difficult to enroll numbers of patients to really show what one wants to show.

[Slide.]

So, we have talked a little bit about general pediatrics, and then I am going to move on to some of the issues related to general oncology. In that respect, I want to focus on endpoints because it really is the main point of today's meeting.

[Slide.]

Before I do that, I just want to mention that there are two types of approvals, if you will, and those are related to the types of endpoints that are being evaluated in primary efficacy trials.

There is regular approval, we refer to this as RA oftentimes. RA is not for retinoic acid, but regular approval in this setting.

Products can be approved on a regular approval basis if they show a direct measure of clinical benefit, such as longer life or in diseases that don't have a mortality outcome and proved symptomatology, such as rheumatology trials, or they can be granted regular approval if the drug is studying an accepted surrogate for clinical benefit, and we all know that there are many, many surrogates that are utilized and accepted, such as lowering blood pressure, cholesterol, et cetera.

Then, there is something called accelerated approval, often abbreviated AA. Accelerated approval can be granted if a drug is being studied for a serious and life threatening disease, and it is evaluating an endpoint that is reasonably likely to predict clinical benefit.

The proviso in accelerated approval is that the applicant must further study that surrogate. Usually, it is in the postapproval setting to actually verify and confirm the clinical benefit.

[Slide.]

So, with that, let me talk a little bit about some of the major endpoints that are used in oncology settings, and certainly survival comes out first and foremost. It is considered oftentimes the gold standard.

Survival is measured from, time from randomization to death, and it has, of course, a number of strains including the fact that it is unambiguous. There is much less bias than in using other endpoints, and it is quite precise. We know exactly when the event occurs.

It has its limitations including the fact that it oftentimes requires a large sample size, something that is quite difficult in many of the pediatric settings, and a long followup, and crossover therapy may confound the effect.

If an individual with cancer progresses, they will likely go on to additional therapies, and the impact of the additional therapies may have some implications for evaluating the outcome of interest.

In trial design considerations, generally,

we need a randomized concurrent control group to really determine and evaluate survival. Progression free survival is oftentimes used in oncology settings. It is time from randomization to progressive disease or death.

The strength of this outcome measure is that it usually entails a smaller sample size and a shorter duration of followup than would be needed for survival, and the differences are not obscured by secondary therapy.

Once an individual progresses, they have reached their endpoint, they are off study, they can go on to additional therapies, and that is an off study. But they have reached their endpoint, they go on to additional therapies, and so there is not this problem with the crossover.

Limitations to this kind of measure is that it is very important to have appropriate methods to determine disease progression, and this is an issue that we will hopefully get into later on today in terms of measurements on patients with brain tumors whether it is a methodology and how

precise can we determine disease progression.

It also has much greater potential for bias in determining when an individual progresses.

Trial design considerations, similar to the survival outcome, generally requires a randomized, blinded, control arm. Because most of the oncology therapies cannot be blinded, though, we have lately been much more involved in our drug companies with the development of independent mass radiographic review panels to actually assess the outcome.

Then, it is very important to evaluate all patients using the same tools at the same schedules.

Then, finally, response rate has a number of strengths as well and the fact that tumor shrinkage generally is taken to be evidence of a drug effect. The caveat I think in particular with patients with brain tumors is that things such as radiation and steroids may actually have some confounding ability to directly determine the response rate.

The limitations; similar to the PFS outcome, there need to be reliable methods to measure it, there is a lot of questions about what is the clinical meaning, and it is going to depend really on the disease setting whether or not response rate confers a type or can reasonably be considered to lead to a clinical benefit.

It is very important when you are looking at response rate to make sure that there is a durability component attached to it.

Trial design considerations, this is one of the outcome measures that usually can be established in a single-arm trial. It is important to make sure that the definition of response is prospectively determined whether or not one is looking at complete responses, or complete responses plus partial responses, or some variation of that theme.

[Slide.]

Then, finally, I just want to mention that in the oncology office, we have had a number of your projects to develop guidances for endpoints.

There is a general endpoints guidance document that is in development. I know you have all received copies of it in your background information.

The draft was out for public comment. We received comments back and now those additional comments have been incorporated and there is another draft that is in circulation and we hope to be able to issue that document in the near future.

We have also then developed a project to look at disease-specific guidances, and on this slide is a list of the number of disease-specific areas that the Office, as a whole, has started to look into.

There has been a process for this, which is first holding a public workshop to solicit input from experts and then to take that input from the workshop and take it to ODAC, the Oncology Drugs Advisory Committee. That is the only committee that is basically legally developed to actually specifically advise the FDA.

I have highlighted the last two disease areas, acute leukemia and brain tumors, because, of

course, those are two areas where there is significant overlap between both adults and pediatrics, and I will come back to that in a minute.

[Slide.]

So, we have talked about general pediatrics, we have talked about general oncology, and going up my pyramid, how does that effect or what is important to know about that with respect to pediatric oncology as a whole.

[Slide.]

I have a couple comments about that. First of all, this whole issue of extrapolation is difficult in many pediatric settings and in particular I think in pediatric oncology, because many adult cancers do not occur in children and vice versa. Therefore, the ability to extrapolate the data from the adult experience is quite limited.

There is a lot of hope that this may increase when and if there is greater understanding of tumorigenesis and mechanisms of action

especially now with a lot of effort at molecular targets, but that is still a work in process.

Like many other pediatric settings, the oncology community and pediatric oncology is thankfully very small in terms of the patient populations. Most of the diseases, if not all of them, are orphan indications. Therefore, studies may be difficult to enroll and take a long time to complete.

Then, there could be competing priorities. If there are a number of potentially active drugs that are potentially interesting to study a particular disease, it may not be possible to evaluate all of them in an expeditious manner, and the NCI, COG, et cetera, I know have to think carefully about how to prioritize because the human resources are so scarce.

And then impact of BPCA, the Best Pharmaceuticals for Children's Act, has a role and we will get into that as well in just a minute, I will have an example for that. It does help provide information in drug labels.

[Slide.]

Similar to the overall issues and endpoints in cancer, the same approval mechanisms apply to pediatric cancer, the regular approval and accelerated approval if there is a surrogate reasonably likely to predict benefit.

The same efficacy endpoints in general are applicable to pediatric oncology, survival, progression-free survival, response rates, et cetera.

I mentioned the two workshops that have some relevance to pediatrics that have already occurred are the Adult Leukemia Workshop, which was held in June of 2005, and that included a lot of discussion about pediatric ALL and AML. I would say that the discussions in that workshop were quite relevant regardless of what age population you are talking about.

In contrast, the Brain Tumor Workshop that occurred in January of 2006, and you will hear a summary of that from Dr. Larry Kun shortly, did not address the unique issues related to children with

brain tumors, including such things as the heterogeneity of the tumors, the significant differences across the ranges of ages and the impact on various types of treatment and long-term sequelae.

Those type of discussions that didn't occur really is what prompted most of you and or many of you at this table to ask about whether or not we can actually hold a specific workshop devoted to pediatric patients with brain tumors, and that was the genesis of today's meeting.

[Slide.]

So, we have talked about now a number of aspects of my triangle, so that brings us then to the main topic at hand, which is pediatric brain tumors. A couple of words about pediatric brain tumors, because you are going to hear about the subject matter experts in just a minute.

[Slide.]

There are many drugs that are used to treat children with brain tumors. These in general tend to be older drugs right now and they tend to

be used off label. In fact, there are a number of drugs that are being used, but most of them do not have specific pediatric indications or data specifically relevant to pediatric oncology in these labels.

That was then and so this is now. Moving forward, I think there is a great amount of interest to study new agents in a number of pediatric diseases with the primary goal to identify and license effective drugs to advance the field.

A secondary goal would be even if these drugs prove to be not effective or too toxic to be used, to basically be able to use that data, and BPCA is a good incentive for that, to enhance the pediatric information that is in the label.

[Slide.]

As an example, this is taken from the Pediatric Use Section of the temozolomide label. Temodar, as probably people are aware, is approved for use in adult brain tumor patients. The labeling specifically says adult astrocytoma and

adult glioblastoma patients.

As people are very aware, it is used quite a bit in pediatric brain tumor patients. The Pediatric Use Section of the label specifically states that Temodar effectiveness in children has not been demonstrated and then it goes on to describe the two open label Phase II trials that were conducted as part of BPCA, and the types of patients that were included in those trials, and conclusion that the toxicity profile in children is similar to adults.

It is a very, very typical kind of information and wording that comes through BPCA, and while it is important and useful information, I think I would submit that what the field really needs is to really identify effective therapies.

[Slide.]

So, today's meeting is going to include, as Dr. Link already mentioned, a number of presentations and then following our open public hearing, we are going to spend the rest of the day having a discussion on this topic.

[Slide.]

We have developed a number of questions for this committee to think about including the value and pitfalls of developing risk based categories, possible patient-disease related factors to consider for such categorization, primary efficacy outcomes for licensure, specific issues related to neurological toxicity including what to measure, how to measure it, and when to assess, and potential settings for non-inferiority studies.

Here, we are thinking mostly about agents that may be intended to reduce toxicity while being able to maintain efficacy.

That is my segue then into introducing Dr. Rajeshwari Sridhara, team leader in our Division of Oncology Drugs, to talk about some of the issues related to non-inferiority design.

Thank you very much for your attention.

Non-Inferiority Trial Design

DR. SRIDHARA: Thank you, Dr. Weiss.

Good morning. I will be presenting some

of the challenges in designing non-inferiority trials for evaluating treatment of cancer.

[Slide.]

In a superiority study, one is trying to establish that the new drug T is better than a placebo or an active control C.

The control in this case may or may not have established efficacy. In non-inferiority trials always the new treatment T is compared to an active control C, and the object is to establish that the new drug T is not much less effective than the control.

In this case, the control must have established efficacy. Non-inferiority does not imply that the two are not different or that they are similar.

[Slide.]

The main object is to demonstrate efficacy in clinical trials with new drug products which are conducted with the intention of marketing the new product.

Two types of claims can be made in such

studies, a superiority claim or a non-inferiority claim.

A superiority claim is the first or preferred choice where the evidence is established directly. A non-inferiority claim, on the other hand, is not the preferred choice and the evidence is established indirectly; that is, there is no direct comparison to placebo here and it is assumed that the control has an effect, and the interpretation could be misleading.

In other words, a non-inferiority claim implies that the effect of the treatment and the control are close.. However, this effect could be beneficial or not beneficial; hat is, if the control is no different from placebo or worse than placebo, then the treatment is also no different from placebo or worse than placebo.

[Slide.]

There are three basic assumptions in considering a non-inferiority study. The first one is that the control has a demonstrated beneficial effect and therefore cannot be another experimental

therapy.

Secondly, we can reliably estimate the control effect size, and thirdly, what we call as the constancy assumption, the control effect is the same now as it was before; that is, whatever was in the historical trial as the control effect continues to be so even in the current trial despite a change in time; that is, the population patient care, et cetera, have remained same over the time period.

[Slide.]

There are two options for designing a randomized controlled trial, namely, to either test the superiority hypothesis or a non-inferiority hypothesis. If the belief is that the new treatment T and the control C are similar, then, a non-inferiority study is more appropriate.

On the other hand, if the belief is that the T is superior, then, a superiority study is more appropriate.

[Slide.]

In a non-inferiority trial, there are two

aspects that are important--I am sorry, I think I skipped one, so I will go back and talk about this.

In considering a non-inferiority trial, three items have to be prespecified, the primary endpoint of the study as presented by Dr. Weiss, either/or a progression-free survival or response rate, and the control effect size and the percentage of this effect size, a size that is to be retained.

Now, I am to the slide.

[Slide.]

In a non-inferiority trial, there are two aspects that are important to be considered. First, how well we know the effect of the control, is the estimate of effect based on one trial or several trials, and what were the size of the trials.

Second, how much of the control effect can we afford to give up, for example, can we give up 25 percent, 50 percent, or 75 percent of the effect.

Furthermore, when the control effect is

estimated based on limited data, retaining at least a delta percent, for example, 50 to 75 percent of the control effect will likely ensure that the new treatment is better than placebo.

In the next couple of slides, I will explain some of the terminology that is used in clinical trial designs.

[Slide.]

In a superiority trial, the null hypothesis is that there is no difference between the treatment and control or the hazard ratio is 1. The alternative hypothesis in this case is that the hazard ratio of treatment to control is less than 1.

The premise of conducting clinical trials is to reject the null hypothesis on the observed data in order to prove the alternative hypothesis. That is, we are always interested in showing that there is an effect.

[Slide.]

In a non-inferiority design, the null hypothesis is that the hazard ratio of the new

treatment T to the active control C is larger than a margin M versus--for example, we could consider an alternative hypothesis that the hazard ratio is 1, meaning that the efficacy of T is similar to that of C, or T is slightly better than C. Then an alternative hypothesis with a hazard ratio of 0.95 can be considered.

The margin M is determined based on the estimated active control effect size and the percentage of this effect that is needed to be retained. Again, by rejecting the null hypothesis, one establishes non-inferiority between the treatment and the control.

[Slide.]

Non-inferiority implies that the new treatment is not much less effective than the control. Suppose X is the effect size of the active control, for example, suppose the point estimate of the hazard ratio of the control to placebo is 0.5. This implies an estimate of the active control effect size is a 50 percent reduction in the risk of event.

The term "percent retention" is percentage of the control effect size X that is retained. For example, 50 percent retention of the 50 percent effect size is 25 percent effect size. In other words, the putative hazard ratio of treatment to placebo, if we were to conduct a trial with the placebo, then, the hazard ratio of treatment to placebo we assume to be 0.75.

[Slide.]

As a first step, we need to estimate the size of the active control effect. From a given study or studies, we generally describe the effect by a point estimate and a two-sided 95 percent confidence interval.

We can say that 95 percent confidence limit that the true effect is anywhere between these two confidence limits. Potentially, we can consider four approaches to estimate the true control effect.

If we choose the point estimate as the active control effect, then, this will inflate the false positive rate. On the other hand, if we

choose the other extreme, that is, the lower 95 percent confidence limit as the estimated control effect, then, the false positive rate will be very small.

A compromise is to use a lower gamma percent limit as the estimated control effect which will ensure that the false positive rate be 0.025, for example. Choosing a fixed margin approach, such as the hazard ratio is greater than or equal to 1.2 is quite arbitrary.

Whatever we choose as our estimate of the control effect, we have to then decide on how much of that effect we are willing to give up, or, in other words, how much of that effect we feel compared should be retained by the new drug.

[Slide.]

There are several methods used to estimate active control effect size, and every method makes assumptions that are not verifiable. In the absence of verification, generally, a more conservative method is preferred. No method is ideal and no one method is endorsed by the agency,

and all methods have some limitations.

[Slide.]

I will now present a hypothetical example of a non-inferiority trial design. Suppose we know from historical trials that the point estimate of the hazard ratio of placebo to control is 2.0, that is, a 50 percent reduction in risk of death with control compared to placebo, and the 95 percent confidence limit is 1.9 to 2.1, therefore the true effect may be anywhere between 1.9 and 2.1.

Then, for example, arbitrarily choosing a 70 percent confidence interval, the lower 70 percent confidence limit is 1.97.

[Slide.]

Iterating the choice of the estimate of the effect size, as seen in this figure, the point estimate of the hazard ratio is 2, the lower 95 percent confidence limit is 1.9, and the lower 70 percent confidence limit is 1.97.

[Slide.]

Now, suppose we want to retain 50 percent of the control effect; that is, if the trial could

be conducted comparing treatment to placebo, then, we expect that the hazard ratio of placebo to control would be 1.49. In this trial, we don't have placebo, but this is our assumption.

Suppose we can accrue 100 patients per unit time, and our alternative hypothesis is that there is no difference between treatment and control, or that the hazard ratio is 1, then, we need a minimum of 407 patients, all followed until death, or roughly 1,000 patients until 407 events are observed.

On the other hand, if the alternative hypothesis is that the treatment is slightly better than the control, that is, the hazard ratio of treatment to control is 0.95, then, fewer patients will be necessary.

[Slide.]

Apart from the magnitude of the active control effect size and the percent effect to be retained, the sample size depends on how good the historical data is, do we have only one study or many historical studies if there is only one

historical study, then, the confidence interval for the hazard ratio will be large, that is, there will be more uncertainty about the effect size.

In summary, superiority trials provide direct evidence a new drug can be compared to placebo or control.

Non-inferiority trials provide indirect evidence, and the new drugs must be compared to established control, and the interpretation could be misleading.

[Slide.]

For non-inferiority trial consideration, active control effect must be well characterized, that is, we should be able to estimate the effect size, and the control effect is same now as it was before.

The non-inferiority trials are generally large. Sample sizes for a non-inferiority trial is dependent on the magnitude of the control effect, population, percent retention, and the alternative hypothesis.

[Slide.]

Finally, in considering non-inferiority trial, any potential loss of efficacy must be weighed against risk-benefit ratio, and failed superiority does not imply non-inferiority.

Thank you for your attention.

DR. LINK: If there are immediate questions, we will continue with the agenda, and Dr. Larry Kun from St. Jude will present a summary of a meeting that was held in January about clinical trial endpoints in primary brain tumors, both pediatric and adult.

The committee members should have received and have read the minutes of that meeting.

Summary of January 2006 Workshop on Clinical Trial Endpoints in Primary Brain Tumors

DR. KUN: Thank you Michael.

[Slide.]

I would like to summarize this meeting. Karen has already given you the introduction to the meeting that took place now almost a year ago.

[Slide.]

The purpose of that meeting was to

consider the pros and cons of a number of different endpoints in clinical trials relative to approval of drugs for primary CNS tumors.

The goal was about advising and establishing a set of principles on current and future standards, and the focus throughout the meeting really was on endpoints that could now or in the near future be incorporated into such trials.

I think it is fair to say that although the goals initially were announced for both adults and pediatric gliomas, for a variety of reasons, including Karen's statement earlier, and the knowledge that the FDA was considering a pediatric meeting of this nature, the focus really was almost entirely on adult tumors.

[Slide.]

The agenda for the meeting included an introduction relative to the FDA and its goals and requirement by Rick, and then the regulatory background, similar to what Karen has shown us, by Ed Rock.

Howard Fine presented an overview and I will show you just one or two slides from that regarding classifications, the variety of therapies available in adult gliomas, and the issues related to some of the efficacy endpoints.

We then had a series of discussions related to imaging-based endpoints, and I will summarize those briefly, with regard to MRI, and PET studies, as well as correlations amongst the imaging responses and progressions, and subsequent survival endpoints related both to the NCCTG and NABTC trials.

Finally, there were discussions regarding cognitive testing and quality of life endpoints, Christina Meyers, who is here today, and I will summarize some of her material, and then some information and discussion regarding biomarker endpoints and research priorities.

[Slide.]

Since we deal with somewhat different classifications, it was of interest that the classification that Howard has proposed and

utilized in some of the Neuro-Oncology Branch trials really separates Grade 1 tumors from Grades 2 through 4, perhaps inappropriate categorization in adults that I don't think relates quite as well to pediatrics where most of us would categorize Grade 2 tumors as low grade neoplasms.

[Slide.]

I think the challenge here and repeated several times during that session, and I suspect here today, relate to the variety of endpoints including survival, disease stabilization, clinical response as it is separate from radiographic response, and then quality of life endpoints.

[Slide.]

Jim Provenzale, a neuroradiologist at Duke, presented both information, as well as examples of MR imaging and utilization in measuring response. Clearly, MR has become widely available and is considered the preferred imaging modality because of its sensitivity, the fact that one can systematically use 3-dimensional data in looking at tumors. MR is complex in comparison to prior CT

data and the ability to technically reproduce the same parameters in doing MR studies across multiple institutions is a consideration that was raised in the context of this meeting.

Key here are some of the endpoints. These have been discussed and published as well with regard to size and how one measures size, and I will show you some information on that shortly, as well as the degree of enhancement, clearly indicative of alterations in the blood-brain barrier are used as a measure of both progression and response to therapy. Most of us recognize susceptible to differences in the contrast dose, the administration and the time between administration, and image acquisition.

[Slide.]

Several newer, what we in pediatrics I think you have to refer to as investigational imaging parameters, were reviewed as well.

Some of these have been studied more consistently in prospective trials in the adult community and were reviewed with regard to MRI

spectroscopy, looking at metabolic profiles and linking those to now anatomically defined volumes, MR diffusion, basically, the rate of diffusion of water molecules within a tumor. This is felt to be a valid measure of therapy-induced changes, and I will show you examples of that in just a moment with regard to response, and MR perfusion meaning blood volume and permeability measurements within a tumor.

[Slide.]

I am adding examples just from the pediatrics here quite briefly. This is some data acquired in limited volumes in a Phase 1 trial in PBTC, but looking at diffusion ratios and documenting the fact that one saw a reduction in diffusion ratios before and after irradiation.

This is shown to you here with diffusion here prior to and subsequent to irradiation, which is an indication in brain stem gliomas, a key interest within pediatric neuro-oncology that right after radiation therapy there is some swelling within the tumor that diminishes diffusion.

[Slide.]

Again, if one looks at limited, again, in a Phase 1 setting, one can see that diffusion ratios over time are stable for patients who are clinically stable, and decrease as a matter of increased tumor cellularity in patients who show disease progression.

[Slide.]

That is indicated to you here with diffusion showing a decrease in perfusion that is associated with tumor progression based upon other imaging and clinical parameters.

[Slide.]

Perfusion measures tend to increase gradually over the course of disease in brain stem gliomas in kids, and you can see that the ratio increases in both patients who are stable, as well as those documenting progression.

[Slide.]

You can see this is a measure here of increased perfusion associated here with tumor progression.

[Slide.]

Second separate imaging parameters in prospective trials in adult patients with gliomas relate to FDG-PET. This is a quantitative measure of tumor burden. It reflects the metabolic activity within a tumor.

The standard uptake values or the quantitative measures of FDG-PET activity are used in PET measures in different tumor systems and tend to be relatively more difficult in the brain because the brain itself is so metabolically active that the difference between a tumor and the underlying activity of the organ is much less than it would be in other solid tumors, for instance, in children.

Technical factors regarding PET imaging do complicate serial and cross-institutional quantitative measures, and so at least to date, the ability to look at multi-institutional trials with PET imaging is quite limited in adults with gliomas.

[Slide.]

There was considerable discussion regarding the endpoints of imaging progression and their implications for survival. The data that was presented at the meeting from the North Central Cooperation Group showed in fact that there were multiple comparisons regarding the standard utilized RECIST criteria and the WHO criteria--and these are backwards here, I am sorry, as far as unidimensional and the multidimensional or bidimensional measurements rather that do reflect the RECIST criteria--as well as comparing these to computer-calculated area and volume parameters which were done centrally within the NCCTG.

The agreement trying to look at single dimension, bidimensional, and volume parameters was moderate across these studies. The difference between single dimension and bidimensional was zero, there were quite equivalent. When one then tried to compare these to volumetrics, it was quite difficult to show that comparison.

From the standpoint of actual response, that is reduction, a positive response, there was

no real association between that response and survival, and on the other hand--and I think the bullet here is that the relationship and between progression-free survival measured at 6 months and overall survival measured at 12 months, in a series of Phase II GPM trials, was quite positive statistically.

[Slide.]

This was just published this month. It's available as an electronic pre-publication abstract to neuro-oncology, and it is the same data really that Dr. Ballman had presented at the meeting in January.

The numbers are shown to you here. There were quite a large number of patients treated in a Phase II setting with newly diagnosed GBM, a modest number, on a number of Phase II trials for recurrent GBM, and the correlations between progression-free survival and overall survival statistically were quite strong.

In fact, the endpoint of the discussion in January in this publication is that

progression-free survival at six months was recommended as a reasonable endpoint for Phase II GBM trials.

[Slide.]

This data was corroborated by a similar number of multiple trials that were studied, 13 Phase II trials from the NABTC Adult Consortium, and looked at progression-free survival status at 9, 18, and 26 weeks, and they together strongly predicted survival time.

The implication here, as Karen had suggested earlier, is that a Phase III trial in glioblastoma, using progression-free survival at 6 months required a much shorter time interval, 1.5 years of accrual versus 3.5 years if one was looking for overall survival in anaplastic astrocytomas, and 2.5 years--I am sorry--1.5 versus 3.5 years in anaplastic astrocytomas if you went from progression-free survival at 6 months to overall survival at 1 year, and 2.5 years versus 4.2 years.

In the anaplastics, we have got these

backwards. I am sorry, the first numbers are for GBM, my apologies.

[Slide.]

In discussion, there were clearly some points raised. Most of us recognize there are changes post-irradiation that confound our ability to quantitatively measure tumors amongst the infiltrating glial tumors, and the suggestion from this session was to basically discount the immediate post-irradiation scan in favor of a baseline two months later for subsequent comparison.

[Slide.]

There was considerable debate regarding whether any imaging modality or series of modalities were really validated as far as efficacy assessments with convincing multi-institutional data using 1D or 2-dimensional measurements in contrast-enhancing tumors correlating progression-free survival.

It was felt that despite the difficulties in cross-comparisons with imaging, and some of the

debate regarding time frame and imaging parameters, that across the large number of patients that were presented from the two groups that I demonstrated to you, that there was fairly convincing data that one could, in fact, utilize the imaging parameters as a basis for progression-free survival in most of the systemic agents that were being tried in malignant gliomas.

Obviously, there is tremendous interest in local modalities including the convection-enhanced delivery trials, and so far the parameters, insofar as evaluating imaging endpoints are really available, so one would really need to use survival in those settings.

[Slide.]

It was brought out that all studies that report imaging endpoints of progression-free survival do combine this with neurologic stability. There was a fair amount of debate regarding the validity of physician assessment as a clinical judgment, and it was felt, in fact, I think in the summary statement, that one had to be

neurologically stable, on stable doses of steroids relative to a documentation of progression-free status based upon imaging.

[Slide.]

There was question, in fact, raised whether freedom from progression itself constitutes a clinical benefit to the patient from the standpoint of the ability to maintain or reduce steroid doses in a setting of adults with malignant gliomas, as well as the necessity to go on or the opportunity to go, as you wish to look at it, on to Phase II or Phase I trials with their own toxicities, leading one to suggest that the freedom from progression does constitute a clinical benefit.

[Slide.]

There was discussion that Christina led regarding clinical trials endpoints related to patient-reported outcomes. Cognitive function, this is an area of intense interest in pediatrics as it is in adults with gliomas.

Tumor-specific symptoms, the availability

of quality of life instruments measuring general QOL measures and health-related QOL measures, and how one took into account the self-reported symptom assessments that were part of the QOL measures, looking toward serial measures of symptoms and health-related QOL assessments and their implications.

Composite endpoints regarding patient functions and neuroimaging were suggested as a potential outcome measure. These have not been documented to this point in time.

The value of steroid reduction as an endpoint, in itself, as I mentioned earlier, I think is something which is considered in the adult trials, and the patient-reported outcomes used as a basis for approval was highlighted in neurology and psychiatry-based drugs, all of which have been based upon Phase III blinded trials in those settings.

[Slide.]

Clinically meaningful endpoints for patients with brain tumors, Howard had summarized,

is survival. This is sort of absolute.

Progression-free survival, where we raised questions earlier, but felt to be as a surrogate for other clear benefits.

Radiographic response as it might relate to clear benefits in survival otherwise documented.

And clinical response and quality of life are yet to be further developed.

[Slide.]

There were highlighted some of the parameters that have been used for FDA approvals in adult malignant gliomas including those parameters which were noted in a Phase III trial for Gliadel with 2 to 3 months survival advantage in newly diagnosed or recurrent GBM, data with which most of us are familiar with temozolomide, looking at the advantage in Phase III studies, and then, of course, questions asked regarding the therapeutic outcomes and how clinically meaningful these might be in patients with gliomas and trying to contrast statistical significance and difference with clinical significance and difference, which is

obviously not a simple thing to do in that setting or some of our own. Then, of course, bringing us back to what clinical trial endpoints are representative of those outcomes.

[Slide.]

For those of you not familiar with it, I am simply repeating here the Phase III European studies upon which the decisions were made with reference to temozolomide, looking at irradiation plus or minus temozolomide in large Phase III studies, that are shown to you here, regarding overall survival and progression-free survival.

[Slide.]

As a challenge, several of us here had been involved in a CTEP originated or initiated workshop on brain stem gliomas where some of the same survival characteristics are noted and one looks critically at how one might measure outcome and potential efficacy or progress in the brain stem gliomas.

Malcolm had organized that meeting in May 2006. Part of that meeting, Arzu Onar, a

biostatistician in PBTC, had looked at the data which has been disappointingly consistent over most of our careers for those of us sitting around the table in pediatrics, showing here very, very strictly defined unfortunately survival and progression-free survivals which has relatively little variability.

I guess one of the challenges that we may discuss as we go through the workshop here today is this is another analysis from the PBTC data that combines patients, about 37 patients who stayed on study, but showed no progression or were never called progression, looks at overall survival, compared to patients who did document progression, about 67 patients, and then compares that survival with patients who went on to Phase I and Phase II trials at the time of recurrence with brain stem gliomas.

Obviously, all of them, number one, have the same outcome. Number two, we don't see any bump related to the Phase I studies largely within the PBTC, impacting survival, and this has some

implications as we look at progression-free survival and overall survival endpoints in the context of pediatric tumors.

[Slide.]

Just to summarize some of the subsequent data from the January meeting that I think is relevant here with regard to cognitive dysfunction, and these are slides that I have borrowed from Christina.

Net clinical benefit of cancer therapy was felt to include beneficial effects on disease-related symptoms and quality of life. Maintaining function is particularly important since long-term remissions or cure are unlikely in the adults with malignant gliomas in some of the settings in which we deal with pediatrics.

[Slide.]

To quote here, "radiological response alone is not acceptable for approval. However, improvement in neurocognitive function or delay in neurocognitive progression may be acceptable endpoints."

[Slide.]

Obviously, there has been a lot of discussion including that in pediatrics regarding tests of quality of life, cognitive function.

Their availability, the consistency with which they are acquired, as well as the variability in those testings, and consideration of normal versus altered cognitive development after treatment in long-term survivors, which can only relate to some of those tumors in the pediatric session where we do, in fact, see long-term survivorship.

[Slide.]

There were some interesting discussions at the end of the session, particularly amongst the patients and family representatives who were there, questions regarding the benefit of extending survival that might be overestimated in a setting where the patients' neurocognitive function is seriously compromised and the quality of life is poor.

This is a question I think that we deal

with in several different settings in pediatrics and certainly a major question in adults with malignant gliomas. There was a very provocative patient representative who basically reviewed his own experience in caring for his wife with GBM for 18 months, confirming for him that survival alone is not a good outcome measure and that unless one can correlate survival with quality of life, that one was not necessarily measuring a meaningful outcome with regard to the efficacy of intervention.

I think that summarizes the points from that meeting, as well as obviously some pediatric editorial comments.

DR. LINK: Next, we will go to Mark Kieran from Dana Farber, who will talk about biology of pediatric brain tumors.

Biology of Pediatric Brain Tumors and the Heterogeneity of this Disease

DR. KIERAN: Good morning.

[Slide.]

I was given the objective today of

discussing a little bit about reviewing the biology of pediatric brain tumors in particular with respect to whether or not adult and pediatric tumors of the central nervous system are, in fact, similar or different and how that may impact on the applicability of adult studies regarding both safety and efficacy for drug approval and use, and then a brief discussion of some of the endpoints and, to a lesser extent, trial design that may help guide some of what we do in pediatrics.

[Slide.]

I have arbitrarily broken this into four segments. The site of origin of the tumor and the histology appear to be very important components that kind of relate to some of the issues of pediatric brain tumors.

I won't talk about the presenting symptoms since those are often related to the site of the tumor, and I won't talk about dissemination. Although these are very important in pediatric tumors, dissemination is often a result of the histology, and therefore, to some extent, they are

built in.

[Slide.]

So, what I will do is talk first about disease site or location, and I am going to just break it up into a couple. Again, I am going to give very general overviews. There is, in fact, a paucity of data that really allows one to understand in detail these differences, but if we take, for example, glial tumors in pediatric versus adult, and even within pediatric patients themselves, we understand that location is probably important.

If you look at the brain stem, for example, the difference of having a glioma in the pons versus outside of the pons, either the medulla or brain stem, and even tumors, the medullopontine and midbrain pontine tumors that are within millimeters of where a diffuse pontine glioma would be expected to occur frequently have a very different pathology even though they don't always have a different histology.

Malignant tumors of the pons, for example,

in pediatrics versus the same grade of tumor in other parts of the brain, many diffuse pontine gliomas, for example, will be Grade 3 tumors, but behave significantly differently from Grade 3 tumors in many other places, which, as you just saw from Larry's presentation, a very poor prognosis; that bithalamic tumors, so there are some patients with bithalamic low grade gliomas, well documented on histology, that have a virtually, universally fatal outcome.

By contrast, there are many patients with very large, optic radiation, optic pathway, and chiasmic tumors that can be, in fact, much, much larger than these for which the prognosis is, in fact, very good. So, it is not just having bilateral tumors or very large tumors, it appears that the location is important.

In pediatrics, in particular, this concept of diencephalic, for what would be an otherwise relatively easy tumor in most other circumstances, by virtue of involvement of the hypothalamic and thalamic structures, can cause a very unique

syndrome and difficulty to treat.

With respect to the neural tumors, it is not recognized, in fact, that location is critically important. What were once referred to all as PNETs of the central nervous system, we now recognize that posterior fossa tumors are uniquely different, medulloblastoma, and even within medulloblastoma, for those at the most recent SNO, there is some indication of whether there are different medulloblastomas that occur out into the fourth ventricle versus those that occur within the parenchyma.

Certainly, many pediatric oncologists in the room, even if it's not yet part of the standard classification schema, are beginning to see and treat large cell medulloblastoma and anaplastic medulloblastoma as diseases different from desmoplastic or typical medulloblastoma.

Similarly, while we used to lump all of these are just PNETs, the sense that pineal blastomas may, in fact, be different from supratentorial disease is again raising the

question of separating out some of these components.

So, for both glial and neural tumors, what used to be thought of as more uniform diseases are becoming more different.

[Slide.]

The classification scheme of Grade 1, 2, 3, and 4 astrocytoma, clearly histology is important, I think there is no question of that, although as you already heard from the prior presentation, in pediatrics where we really see 1's and 2's as a group, and 3's and 4's as a group, already differentiate this a little bit from the adults.

Obviously, the sampling error for many tissues, since you only get a small piece of it, what we call a Grade 2 may be a Grade 1 or a Grade 3 depending on the pieces taken, and that obviously adds to the complexity of any analysis and for which we can't easily control.

Again, this concept of diffuse pontine gliomas Grade 3s in this location versus in this

location suggests that histological subtype can be important. I think Ian is going to present some of the work from the recent reporting at SNO for the A9952 study in which low grade gliomas, which have a relatively good prognosis in pediatrics, but a clear difference between patients with NF1 versus without NF1, in spite of the fact that the neuropathologist can't see any difference between those two lesions.

Again, regarding histology, here is a kind of reverse example. It is not clear that Grade 2, what were sometimes referred to, I think inappropriately as benign ependymoma versus anaplastic ependymoma Grade 3, in fact, disease for disease, metastasis for metastasis, have any difference in actual outcome or therapy except maybe in supratentorial compartments completely resected.

So, here is a circumstance where it is not clear that grade, in fact, makes any significant difference, and many people in the room are probably aware that in 1P19Q, that unlike the adult

series where there is a relatively high incidence of those changes, and a very strong correlation with chemoresponsiveness and outcome, in fact, the incidence of those changes in pediatric oligodendrogliomas is found at a much lower incidence, and the benefit to having those with regard to chemoresponsivity isn't nearly as pronounced, suggesting that pediatric oligodendroglioma may not be exactly the same thing as adult.

Obviously, one of the things that we are trying to define differences and similarities, but I think in many ways, what it may mean is that there is a smaller proportion of pediatric oligos, for example, that fit the adult, but that the majority don't, and we are probably not going to find a single rule that fits all circumstances in all cases.

With respect to histology in neural tumors, there is the Chang staging for medulloblastoma, but by separating out posterior fossa ATRTs, for example, and separating out pineal

blastomas from PNETs and ATRTs of the supratentorial, we have already been able to focus studies to a much greater extent on some of these and identify characteristics.

I think Ian will probably talk about the fact that we are now mandating pathology in part because your risk stratification, and therefore response to therapy, are going to be different by your histologic subtype.

Obviously, the one thing I did want to remind people, I think everyone here is likely aware, choroid plexus carcinomas, craniopharyngiomas, for example, we can't really look to the adult experience to guide us, and therefore, no matter what mechanisms we develop in terms of guiding us with respect to informing on these pediatric diseases in the context of their adult counterparts, that clearly there is going to be a point where some pediatric diseases are going to have to be studied on their own, and we are going to need mechanisms for that.

[Slide.]

Risk stratification by age, which obviously in pediatrics is very important as you already heard, whereas, the vast majority of low grade gliomas in adults will eventually become Grade 3's and Grade 4's, and result in death, in fact, in pediatrics, that is not true. Although our Grade 2 in pediatrics often recur, they recur as Grade 2's and can be dealt with accordingly as Grade 2's.

By contrast, when you look at pilocytic astrocytomas in adults, in pediatrics they appear to be the same, so Grade 1's appear very similar. Grade 2's are probably different and are going to require different strategies.

We know that pediatric low grade gliomas can often be responsive and again, in this audience, response was often determined either by radiographic response or by stable disease, which I recognize as a number of issues.

It is not clear that adult low grade gliomas would respond the same, because I couldn't find any trials that have even tested, but we use

routinely in pediatrics versus what adults use.

There are some clear areas of difference, however, that are documented with respect to pediatric and adult tumors. If we look, for example, at the presence in primary glioblastoma and secondary glioblastoma in adults where they are frequently EGFR or V3 positive in P53 wild type versus the secondary tumors, which are EGFR wild type and P53 negative. So here is a difference in adult primary and secondary, and this has been well published and documented.

By contrast, pediatric patients, we don't see a very high incidence of secondary tumors, so almost all pediatric GBM is primary type, and, interestingly, we don't see the V3 mutation in pediatrics virtually at all, and, interestingly, the P53 mutational status of pediatric tumors is somewhere between zero and 100 percent depending on the study you look at, which tells that we haven't probably worked that out very well.

Obviously, the rarity of oligodendrogliomas in pediatric versus adults, and

the changes I have already talked about, as well as the abundance of ependymomas and particularly of the Grade 2 and Grade 3 supratentorial or infratentorial as opposed to spinal disease, means that even as we begin to learn something in one population, it may not be applicable to the other.

Finally, with respect to the neural tumors, from the most recent German report that I think is now undergoing validation for similar sets in the baby protocols from the prior POG and CCG studies, the sense that desmoplastic, subtypes of medulloblastoma may be an important component with respect to treatment outcome. The same therapy in the desmoplastic may actually be different and therefore we may now have to substratify on that.

Of course, the assumption that adults with medulloblastoma always did significantly worse than their pediatric patients, and whether this was really just the result of the fact that we tended to undertreat adults, they often only got craniospinal radiation as their single treatment.

For those of you that were at the recent

SNO meeting, that was a poster of about 50 adults that got radiation plus chemotherapy, and had a 3- and 5-year event-free survival approaching 75 percent, which, in fact, would approach very similar to what it is in pediatrics. So, in fact, adult may not be different than a pediatric medulloblastoma as long as they are treated near equivalently.

Obviously, the adults got somewhat different chemo because they don't tolerate the same chemotherapy, particularly the vincristine, so it is not a completely fair comparison.

Obviously, the differences may therefore be in the way we treat, and we may be able to remove some of those by virtue to standardizing the treatments, but I think there is also a sense that the differences that we have seen between adult and pediatric tumors may result from the difference in both the origin and the stage of the cancer stem cell that is affected.

Again, this idea that we see certain abnormalities in adult tumors that aren't seen

typically in the pediatrics suggesting they are going down different pathways. I think a lot of work is now beginning to go on in this area.

Finally, there is also the sense that cancer is no longer really just the disease of a tumor cell. Clearly, the tumor cell has a whole environment around it that is required for supporting and maintaining the tumor, and we are beginning to realize that the circumstances in which tumors arise become important.

Work from Josh Rubin in St. Louis, we are looking at NF1 patients with optic gliomas which we know are quite abundant. Patients with NF1 have abnormal expression of CXCR4, and CXCR4 is a neurodevelopmental cytokine pathway that is basically located to the optic pathway and therefore there may be specific developmental cues that give you one tumor in one circumstance that you wouldn't see in another circumstance that I think we are going to have to understand in that context.

[Slide.]

The last part, questions of markers for pediatric CNS tumors, obviously molecular markers of prognosis which would help in diagnosis and treatment--and I think a lot of people are working on this--as well as pediatric classification schemas that are going to have to take in not just histology, but some of the new molecular findings, certainly some of the new neurobiologic findings, and, in particular, neuroimaging.

This isn't actually all that new. These are diffusion perfusion and MR multivoxel spectroscopy of central nervous system tumors. So, to some extent on a somewhat gross level, we have already begun asking some questions about the biology of tumors, not strictly what size it is.

[Slide.]

Obviously this can be combined and fused with PET scanning although I think most of us in the room are not sure that PET scanning is going to be the answer to all nuclear imaging, it certainly provides some functional data that when fused can corroborate some of the changes being observed.

[Slide.]

But I think for many of us, the sense that the molecular profiling of tumors is going to be an important point in terms of figuring out what targets to go after, medulloblastoma versus malignant gliomas versus rhabdoid tumors, normal cerebellum and PNETs in a group of pediatric tumors. I think we all recognize that they are different, and the real question is what are the genes both up, the reds and the blues, that kind of mitigate that as a way of trying to understand how to intercede.

[Slide.]

A large advance in both the proteomic, Maldi and SELDI-TOF profiles of tumors that are now beginning to allow us to ask specific questions about what is the phosphorylation status of that protein in a large number of samples, something that we couldn't do before. I think many programs here are probably developing kind of kinase sequencing programs for many of their tumors in the sense that this may be the way to go, but one

cautionary tale.

[Slide.]

This is an example of VEGF-A expression in a pediatric optic pathway low grade glioma. Tumor cells are very high expressing. In fact, in about 50 or 60 samples so far, all of them are positive.

[Slide.]

When you look at VEGF-R, the phosphorylated form of VEGF-R2 in the vasculature of those tumor cells, it's highly positive, suggesting that there is a paraffin loop here. To some extent that would seem to be a good target, but, of course, we have been down that road before.

This is a sample of a diffuse pontine glioma. Here is the histology. Some areas are very highly expressive of EGFR, other areas that are somewhat negative, areas of infiltrative--I don't know how well this shows up here--but infiltrative cells throughout these that are positive.

But as many of us know, and this has certainly been seen in other studies including

PDGFR in a variety of adult tumors, the fact that there are very marked areas of positivity of these, when you treat them with inhibitors, we haven't seen the kind of responses that would be predicted based on this kind of immunohistochemistry, suggesting that the immunohistochemistry, either by virtue of the fact that there are pathways that will compensate for your effect or that, in fact, that these pathways, although present, are not critical for tumor, we still haven't understood.

I think one of the critical aspects for the development of the program today is going to be how to understand these variances as we try to move forward. I think that is going to be particularly important, as I just said, because as the number of molecules that we can test in the pathways that are involved continue to increase.

It is not a question of whether or not a single drug is an inhibitor will cause shrinkage and how we measure that versus how MRI, MRS, or et cetera, et cetera, it's what do you do for large groups of biologic drugs, and not knowing one of

which may actually have activity only in multiple combinations, can you suppress sufficient numbers of pathways to actually see the effect and in which drug gets the credit for that kind of response as they move into larger combinations.

This is important because as we have seen, there are now a large number of drugs that are available for a large number of these pathways.

I will finish off with--so one of the things that many of the groups have been working on--I was asked to present is a little bit of experimental work--and that is again beginning to ask questions, not just about the size of these tumors, but about the activity of the molecular pathways that are relevant for these tumors.

This is a validation, this is bioluminescence in a positive and a negative, but this tumor has alpha v beta 3, beta 5 activation, this one does not. You can use very specific imaging molecules to pick up this tumor here, but not the tumor on the other side. You can specifically block it with a variety of specific

peptide probes for specificity.

[Slide.]

I won't really go into that for brevity of time. Let me move forward.

[Slide.]

In addition, you can now image and very clear. This is an intracranial orthotopic tumor in which you can now pick up very sensitive imaging of these. This is going to be important because, of course, for alpha v beta 3, as well as for a number of other antiangiogenic and biologic pathways, there are now targets for these that we can begin to use.

[Slide.]

This is, in my last couple of slides, this is an example. Here, you can see a tumor-- wrong angle, so I can't quite see what is up there--here is SPECT imaging that can show these.

If you combine them together, you can see excellent overlap in orthotopically implanted tumors, so we now have the ability to do really relatively defined molecular imaging, and, in fact,

one of these drugs is already in clinical trials in Europe to look at this in central nervous system. It can even pick up relatively small tumors. Here, you can see that there were three small tumors implanted. These are about a millimeter in size each.

[Slide.]

Here is the SPECT imaging using these alpha v beta 3 specific labeled ligands, and again if you overlap them, you can quite easily pick up some of these changes at the millimeter level. This is to show you that these three areas correspond to areas that these cells were also bioluminescently labeled, so that we could be sure exactly where they were.

[Slide.]

Where I think this is going to be even more important, it raises some of the questions about specificity. Here is an animal that had two tumors here.

When you do the SPECT imaging, in fact, you can only find one of them, and again this one

doesn't show up in spite of the fact that on MRI, that would certainly have been I think considered positive disease.

When you compare it to bioluminescent, obviously, something that can't be done in humans, but we knew there was no tumor down here because we didn't put any tumor down there, it is something else, and, in fact, when you do the histology, there was a large inflammatory response there that picks up none of the alpha v beta 3, whereas, this is a solid core of tumor as expected, so the specificity for these is becoming quite good.

[Slide.]

So, in summary, obviously, there are significant differences in adult and pediatrics although many of them are more what we feel than what we really know in part because we have never really done the kind of detailed comparative studies that would be required.

Certainly, some of those differences may be due to the location of the tumor, as well as to the histology of the tumor, and finally, to the age

of the tumor. But as there are increasing numbers of molecular inhibitors, determining the specificity of those targets, which don't always relate to responses, are going to be important design issues.

Therefore, I think what we are really going to start to do as we move forward is look at molecular activities and how those would be integrated into the concepts of approval both for pediatric and adult studies.

I think I will stop there.

DR. LINK: Thanks, Mark.

Next is an overview of the Children's Oncology Group experience by Dr. Pollack.

Children's Oncology Group Experience with Pediatric Brain Tumor Clinical Trials

DR. POLLACK: Thanks. I am going to give an overview of the Children's Oncology Group experience with clinical trials, and my apologies to those in the room who have heard bits and pieces of this talk probably a dozen times over the years.

[Slide.]

What I want to focus on are some of the current, recently closed and soon to open trials just to give sort of a broad overview.

[Slide.]

The overall scientific goals of the Brain Tumor Committee in the Children's Oncology Group are:

To identify biological characteristics of childhood brain tumors that influence treatment response and try to move forward to risk-adapted treatment stratification;

Develop comprehensive treatment approaches to improve the survival of children with primary brain tumors;

To identify effective therapies for tumors that have been resistant to prior treatments, and to come up with strategies for reducing long-term sequelae.

[Slide.]

This slide highlights some of the complexity that is involved in dealing with pediatric brain tumors. I have listed along the

top the most common types of tumors, and this does not include all of the types of pediatric tumors.

There are clearly less common ones, such as choroid plexus tumors, craniopharyngiomas, that we don't have any active protocols that are dealing with, but for each of the major types of tumors, we have a series of protocols that are looking to try to tailor therapy for the good risk tumors either by optimizing the use of chemotherapy to try to delay or avoid the use of radiation, to optimize the use of radiation using conformal delivery, and for some of the poor risk tumors that have been more difficult to treat over the years, combining chemotherapy with radiation and intensifying chemotherapy.

The different studies for the different tumor types are shown going along the table.

[Slide.]

I wanted to briefly mention some of the accomplishments over the years. One of the most important accomplishments for medulloblastoma has been the observation that for standard-risk

tumors--that is, those that are non-metastatic and are completely resected--it is possible to reduce the dose of craniospinal radiation by adding adjuvant chemotherapy.

For many of the tumor types, it has been shown that extent of resection has a major impact on outcome, and that has influenced how these tumors are dealt with at diagnosis.

We have initiated a number of large biological studies for different tumor types including high-grade gliomas, infant tumors, and PNETs.

[Slide.]

This slide highlights the effect of adding chemotherapy on the ability to reduce radiation doses in children with medulloblastoma. The curve in pink or purple are the survival results in children that were treated with 2340 centigray of craniospinal radiation and with a boost to the posterior fossa, but with no chemotherapy.

The blue line shows the results with standard doses of radiation, at least historical

standard dose, 3600 centigray of craniospinal irradiation, and the results were inferior with the lower dose.

The yellow line shows the survival results in kids that received lower doses of radiation plus chemotherapy.

[Slide.]

Another important I guess observation is the role of resection extent as I mentioned a moment ago. This is from high-grade glioma just showing that tumors that are amenable to greater than 90 percent resection have a significantly better prognosis than those that have lesser resections.

Now, this may reflect as much about the biology of those specific tumors than about the role of resection extent, but it does provide a rationale for extensively trying to remove these tumors.

[Slide.]

Other accomplishments, and I will show some of these slides later, that moderately

intensive chemotherapy improves survival outcome for high-risk medulloblastomas, identification of molecular factors to stratify infant tumors, and, in particular, identifying the atypical teratoid rhabdoids subgroup.

It has been shown that induction chemotherapy achieves a fairly good response rate in infants with brain tumors, but that those responses are often not durable, and we have built on that using high-dose consolidation chemotherapy or focal irradiation, and those results seem to have improved outcome.

Unfortunately, despite improvements in the prognosis for some of the tumor types, there are many others that remain resistant and late effects are a big problem.

[Slide.]

I am going to run through the recent and current studies for the different tumor types starting with medulloblastoma, and this is the recently closed study A9961 that randomized between two adjuvant chemotherapy regimens after so-called

reduced dose craniospinal irradiation of 2340 centigray to the neural axis.

I think many people would consider this the new standard dose based on the results from this study.

[Slide.]

These are the results in the two arms, and these were recently published showing about an 80 percent five-year progression-free survival with both arms, which compares favorably to historical data.

[Slide.]

One of the other important observations from this study was that the small subset of patients that got onto the trial and were found retrospectively to have evidence of metastatic disease did particularly poorly, which highlights the importance of a fairly meticulous staging in studies that are looking at reducing the intensity of therapy.

[Slide.]

Another observation from this study was

that histological features are probably a new criteria for subdividing medulloblastomas. In this standard-risk group, the tumors that had histological features of anaplasia had a significantly worse prognosis than those that had classical features, and this is now a new criteria for identifying high-risk disease in our ongoing studies.

[Slide.]

Our current study for average-risk medulloblastoma stratifies patients based on age. For those younger than 8, there is a two-stage randomization, the first involving the dose of craniospinal radiation, the second involving the volume of radiation to the posterior fossa, the boost volume, with the goal of trying to reduce the frequency of hearing loss, which is another late sequelae in children with these tumors.

In patients older than 8, in which the risk from craniospinal irradiation is possibly a bit lower, there is a single randomization for the boost volume to the posterior fossa.

[Slide.]

In both age groups, we are including prospective analyses of a number of biological markers including Trk C, which is a neurotrophin receptor, and erbB2, which is a tyrosine kinase growth factor receptor, as well as multigene expression profiling, and the accrual of biological samples for this study is actually proceeding very well.

The other aspect is the histological analysis to try to identify the anaplastic tumors and put them on a different protocol, so specimen submission has been strongly encouraged.

[Slide.]

For high-risk PNETs, those that are metastatic and completely resected or localized outside the posterior fossa, the recently completed study was a dose escalation of carboplatinums, a radiosensitizer, during radiation to try to enhance the activity of radiation, and this was followed by adjuvant chemotherapy with cyclophosphamide and vincristine, and after the Phase I component of the

study, there was a randomized comparison between the cyclophosphamide and vincristine regimen and the slightly more intensive regimen.

This study has now completed and it has formed the basis for a Phase III randomized study that is looking at the efficacy of radiosensitization as one randomized question, and also looking at the ability of cis-retinoic acid to potentiate adjuvant therapy as a second question.

[Slide.]

The results from the 99701 study have recently been released, and they actually look surprisingly good compared to some historical data. The three-year overall survival is on the order of 80 percent in this high-risk population, and even more interesting, when we stratified the patients based on anaplasia, the anaplastic tumors do worse. The non-anaplastic tumors have almost a 90 percent overall survival, fairly similar to the standard-risk medulloblastomas.

[Slide.]

Now, I am going to talk about low-grade

gliomas. Historically, these tumors were treated with surgery and radiation, and there were a lot of late sequelae in terms of endocrine and cognitive function, and since many of these patients were long-term survivors, there were concerns about second malignancies from wide radiation fields.

So, one of the approaches that has been used over the last 15 or 20 years is to try to employ chemotherapy to defer or at least avoid the use of radiation if at all possible. The A9952 study was a randomized comparison of carboplatinum and vincristine versus a 4-drug regimen, and that recently complete accrual.

There was also a non-randomized arm for patients with neurofibromatosis 1, who just receive carboplatinum and vincristine. These results have been released in preliminary form and show about a 3-year progression-free survival in the overall cohort, and the results are better in the patients with NF1, suggesting as Mark mentioned a few minutes ago, that NF1 tumors are biologically somewhat different than non-NF1 tumors even though

they look identical histologically.

While we are waiting for the results from this study, we have launched two additional studies. One is building on the carboplatinum/vincristine regimen by adding temozolomide, and a second is looking at the efficacy of conformally targeted radiation in children older than the age of 10 and younger children who have progressed after chemotherapy.

[Slide.]

One tumor type where we have made essentially no progress in the last two decades are brain stem gliomas. These are the results of the Children's Cancer Group 9941 study showing a one-year event-free survival on the order of 20 percent, but this could really be any of our recent brain stem glioma studies unfortunately.

[Slide.]

These poor results do provide a very robust natural history controlled data set upon which to build new studies, and we have a series of studies that have gone through that are using

consistent statistical design features to try to rapidly evaluate agents to add with radiation to try to boost the limited efficacy of radiation for these tumors.

So, we have completed a trial of temozolomide on a daily schedule during radiation. Those results are under analysis. We have ongoing study of topotecan, a radiosensitizer, and we will soon be opening a study of gadolinium texafuron. We identified the Phase I dose in a previous study and are now opening this Phase II study groupwide.

[Slide.]

For high-grade gliomas, we also have a sequential study design approach where we have come up with a consistent statistical design and we are trying to apply that in a series of studies in sequence, so we have completed the study of temozolomide on a daily schedule during radiation, and then on a 5-day schedule after radiation with a comparison to an historical control group, the CCG-945 study group.

The plan was to have a second study with

temozolomide plus either another chemotherapeutic agent or an anti-angiogenic or signalling inhibitor.

[Slide.]

The initial results from the 0126 study were somewhat disappointing in that--I am showing the results for glioblastoma here--the one year event-free survival was essentially identical to the CCG-945 study group, and not surprisingly, the results were not all that much different from the adult study from the EORTC, and that was one of the impetuses for our doing a pediatric study.

So, our results essentially validate what they have observed, that there probably is some modest efficacy to using temozolomide in addition to radiation, but not a tremendous amount, but it is an agent that we can build on since it is well tolerated.

[Slide.]

One of the other observations from this study which mirrors the results from the EORTC study, was the influence of MGMT