methylguanine/methyltransferase expression on outcome, and we categorized tumors into those that have high MGMT and those that have low MGMT.

[Slide.]

We also looked at promoter methylation and what was observed was that tumors that had overexpression of MGMT had a significantly worse prognosis than those that didn't, not that the non-expressers had a good prognosis, but that the other ones were particularly poor.

[Slide.]

The current study for high-grade gliomas builds on this study and also builds upon a previous Phase I study within the group, combining temozolomide with CCNU, and this study has also been accruing very rapidly, and there is a third study that's in the queue for development.

[Slide.]

I will change gears and talk about the germ cell tumors. For germinomas, we have a randomized Phase III study that is soon to open that compares standard doses of radiation versus

chemotherapy and reduced doses and volumes of radiation with event-free survival, quality of life, and neuropsych function as the outcome endpoints.

The goal is to see whether we can reduce late effects without compromising event-free survival by using chemotherapy to reduce the amount of radiation that is delivered.

[Slide.]

For non-germinomatous germ cell tumors, there is an open study that involves the use of induction chemotherapy, and then further therapy is subdivided based on the response, so patients that have complete responses go on to radiation. Those that have less than complete responses to chemotherapy have the option of second-look surgery, and then more chemotherapy prior to going on to radiation.

[Slide.]

For ependymoma, we have a fairly complicated study that stratifies patients based on extent of resection, histology, and tumor location.

So, for the subset of patients that have completely resected supratentorial differentiated ependymomas, which is a very small group, they are strictly observed.

For all the other subgroups of patients that have gross total resection, conformal radiation is given, and then for the group of patients that have incomplete resection, a window of chemotherapy is given and then they are evaluated for potential second-look surgery prior to going on to radiation. This study has accrued almost 3,000 patients.

[Slide.]

For infant tumors, which we treat differently, and the age cutoff being 3 for many of our studies, the recently completed 99703 study built on induction chemotherapy by adding intensive consolidation chemotherapy.

Some of the preliminary results from this have been released and are encouraging in that the results from the new study, the CCG99703, compare favorably to the CCG921 study that involved

induction alone, and in individual subsets of tumors, particularly medulloblastomas, the differences are even more striking, 75 percent versus 30 percent 3-year event-free survival.

[Slide.]

One of the other things that has been observed in infant tumors is that the large group of small blue cell tumors can be subdivided. One of the important subgroups are the rhabdoid tumors which have a significantly worse prognosis than non-rhabdoid PNETs, and that has provided a rationale for trying to identify those patients prospectively.

[Slide.]

So, we are including molecular evaluation by FISH for chromosome 22 deletions, INI1 mutation analysis, and also INI1 immunohistochemistry as a way of identifying tumors that may look like PNETs, but actually are atypical teratoid rhabdoid tumors, and then these tumors are going to be treated differently.

[Slide.]

One of the first tumor-specific infant protocols we had was P9934, which looked at M0 or non-metastatic medulloblastomas. These tumors were treated with induction chemotherapy followed by second-look surgery, and then focal conformal radiation, which was sort of a parallel strategy to the use of high-dose chemotherapy.

The patients then went on to receive maintenance chemotherapy and endpoints were both overall survival and also functional outcome in comparison to an historical control group.

[Slide.]

We have separate studies that are soon to open for M+ or metastatic medulloblastoma that is looking at the addition of methotrexate as a randomized question, and then we have a separate study for atypical teratoid rhabdoid tumors that is unfortunately on hold for the moment, but we will hopefully open, that will intensify treatment in these high-risk tumors.

For all of these protocols, specimen submission is mandatory for the biological

stratification.

[Slide.]

Finally, for recurrent tumors, we have pursued strategies looking at interference with tumor signaling, so we have a number of approaches that are looking at interferons with growth factor mediated signal transduction.

We completed a study of Tarceva or R115777--I am sorry--Zarnestra R115777, which had a number of different tumor-specific strata, and that actually accrued very well and closed rapidly. We have a study of Tarceva that has completed, that included both CNS and non-CNS tumors.

We have a study that is under development involving cilengitide, which is an integrin inhibitor, and then a combination study of Tarceva and Avastin that is including both CNS and non-CNS tumors.

Then, as I mentioned earlier with the medulloblastomas, we are looking at cis-retinoic acid as a maturational agent during the adjuvant phase, and this study is in the queue to open.

DR. LINK: Thank you, Ian.

The last talk of the morning will be neurocognitive sequelae of pediatric brain tumors by Danny Armstrong.

Neurocognitive Sequelae of Pediatric Brain Tumors

DR. ARMSTRONG: Good morning.

[Slide.]

When we talk about neurocognitive outcomes in children, when I have done talks to other groups, one of the things that is complicated is that these are very complex problems.

It is a complex issue to deal with because in contrast to other things that we do in child neural development where the mechanism for a particular impairment is relatively clear and we can trace out a pathway as in the case of many of the genetic disorders.

When we begin looking at neurocognitive outcomes in children treated for brain tumors, the mechanisms may be complex and vary, just as Mark and Ian have presented, the variety of treatments that we have, the heterogeneity of what falls into

the class of children with brain tumors, and a whole host of issues about variations in treatment, histology, risk classifications, and the like.

This slide is something that everyone in this group probably needs no introduction to, but these are just some of the mechanisms that we have to be able to consider when we think about the neurocognitive outcomes that may occur in the treatment of children with brain tumors.

Children with brain tumors have genetic risks that are unassociated with the brain tumor. We can have children with genetic risks for fragile X, for Down's syndrome, for dyslexia, for attention deficit hyperactivity disorder, and a whole variety of other things that we now are establishing genetic links.

We can have structural damage either because of the tumor or the surgery necessary to remove it. We have clear evidence of large vessel injury, with stroke, as well as microvascular injury that show up as calcifications as a result of our therapies.

We have got indirect evidence of disruptions in neurotransmitter capacity. This would particularly fall out in the ways that children respond to some of the stimulant medications as a function of their attentional problems resulting from our treatment.

Metabolic abnormalities are probably a mechanism that is linked at multiple levels perhaps starting at the level of the vascular system, but also potentially being affected by oxygen perfusion, the distribution of oxygen and the efficiency of the metabolic system.

Neuroendocrine abnormalities we have known about for a long time because, when we radiate the heads of children, we are also really interfering with neuroendocrine that is most often reflected in growth, but has many potentials that are we have really not spelled out.

The main things that we are concerned about, however, in terms of the mechanisms in the treatment of children with brain tumors in the global area are disruptions in myelin formation

that is presented out to us in the long term as children who fail to develop the same volume capacity, to develop the same systems of myelin formation, fail to trim and prune early systems of neurologic development, and fail to develop the kind of complex structures that are associated with complex behavioral skills and neuropsychological functionings down the road.

It is probably the area that we are most concerned about, and then, as I always say, we get the problems that children with brain tumors still decide to jump out on the back of their parents' trucks and jump off and hit their heads.

So, we have these kinds of things that come along, and we have children who are not getting the opportunity to learn, because they are in our hospitals being treated.

[Slide.]

We also know that there are a whole host of issues related to the disease and treatment, and when I say disease I am recognizing a great deal of heterogeneity. But things like the literature over

the last 20 years has really shown size and location of tumor can have an impact on what kind of neurocognitive difficulties we come into, surgery, where it is, what the consequences of that surgery may be, radiation therapy with great respect to Larry, that has been our biggest culprit over the years in terms of neurocognitive late effects, but certainly not the only one.

Chemotherapy, I am going to list, and we often list chemotherapy as sort of a singular contributor, but I think what we know at this point is that we suspect that there are very different mechanisms with the drugs that we use, often difficult to tease out, because in the treatment, as Ian presented, most of our children are getting combinations of surgery, so we can't tease that out, they are getting radiation of some form or another, and multiple drug therapy.

So, our ability to be able to tease out what is specific to one drug versus the other is difficult. One of the things that is different as a risk factor from adults and children is age at

the time of treatment.

We clearly have data--and I will actually show one of our early studies in a minute--that shows that the younger the child is at the time that they are diagnosed and tsoreated, the greater the range of difficulties they are likely to have, and the more specific difficulties that they are likely to have over time.

Gender is a question that we have in acute leukemia. It is not as clear that that is a risk factor in brain tumors, but we really have not looked at it in any specific detail related to neurocognitive effects, and then issues like shunt, seizures, CNS infections, and a variety of other considerations really make this a complex area to study.

We actually have discussion in the Children's Oncology Group about whether we ought to. It is hard to get patient accrual. The insurance doesn't pay for the studies. Our number of completed studies and a variety of trials is very low, so you have to kind of raise the

question, well, should we be doing this kind of research - is it logical, is it feasible. It is costly and it's challenging.

Well, there is a very simple reason why we ought to, at least from my perspective, and that is children are surviving, and this is a life-long disability issue for them and for their parents. So even though there are multiple challenges, I think it is up to us to be able to find ways to do that.

[Slide.]

We have, for a long time, attributed most of the concerns that we have had related to children to radiation and/or chemotherapy. But, as we reported in JCO last year in a study of low grade pediatric cerebellar astrocytomas, a joint CCG-POG trial, in a variety of areas these children had functional abilities that were within what we would describe as the clinical range compared to typically developing children with no difficulties.

All the three stars there are the ones there, and that is really one of the first studies

where having a tumor removed surgically with no other treatment may be associated with some late effects.

[Slide.]

It raises some questions. Radiation and chemotherapy are the two biggest culprits that we have at this point, and the primary mechanisms that we have to be looking at are, first, damage to small blood vessels resulting in calcification potentially affecting brain metabolism and chemistry.

I will pause at this point and say that as we have seen the presentation so far this morning, our focus in pediatric oncology has been specifically in the neuroimaging area on defining whether the tumor is present, whether we get necrosis, what the margins are, and what the recurrence is.

We have not done the kind of neuroimaging studies that talk about the mechanisms on brain's development in successfully treated children. That is an area for wide-open research.

One of the things that we do have a model, and I will address this is a second, that we are looking at for children treated for brain tumors is that most of our treatment seems to have relatively minimal effects on the structures of the brain that have developed up to the time of treatment.

The primary impact is on disruption of the developing brain from that point on, and this is one of the things that I mentioned a few minutes ago, its impact on myelin formation, its impact on connecting structures, and its impact on the vasculature that promotes metabolic activity that is involved in the normal development that is concerned, and then a variety of other kinds of things - with sensory impairments, hearing, that has been related to acute issues related to peripheral neuropathy. These are the kinds of things that we are concerned about.

[Slide.]

What we have seen over time--this was our low-risk medulloblastoma study from the 1980s--that helped us to really show that we have some

interactions that are concerning for us in children treated for brain tumors.

These were medulloblastoma, and we looked at in this trial children who were of younger age, under 5, versus children who were older, and who either received standard dose or reduced dose radiation, and there was a clear interaction that younger age and higher dose radiation had significant impairment.

When we were able to reduce the dose or treat older children with higher dose, we got roughly comparable kinds of performance, and older children with reductions in radiation therapy actually had better outcomes. We were able to show that in verbal performance and overall intellectual functioning.

[Slide.]

Similar kinds of findings were there particularly for math, but we found that when we wiped out or when we treated children who were younger with higher doses of radiation, that both math and reading were impairments.

This is one of the things where we began to see that the younger the child was, the more global the impact on their developmental function in multiple areas.

The older they got, we got reading performance improved, but math tended to sort of level off in this group, and that was a question early on, what is the mechanism that makes a difference in these two academic outcomes.

[Slide.]

As we have moved forward, we know that the complexity of looking at neurocognitive outcomes is challenging. We have neurosurgical issues where we may have focal deficits, we may have bleeds.

We may have some rare occurrences in subgroups of children like posterior fossa syndrome with mutism and motor weaknesses and impairment that sometimes recovers in a very unpredictable way, but may have long-term consequences.

[Slide.]

We have radiation therapy and mechanisms of delivery, doses, and, as we are beginning to

look at more refined portals and administration, there may be some issues of not having the whole brain impacted, maybe not, but maybe having very specific areas and pathways that are within the selected portal that creates very specific kinds of outcomes that at this point we are not able to tease out because of low numbers.

The possible outcomes that we have had historically, young children treated with whole brain radiation have had significant global intellectual impairment, but we have begun to see in the 1980s that we were really looking at specific impairments that were developmentally in the radiation therapy field, and so we were able to pin this down, not to just look at IQ, but to look at specific functions.

[Slide.]

In the chemotherapy area, we are beginning to learn a little bit, not a lot, but a little bit about specific functions that may be related to specific chemotherapies.

We know very well that vincristine has an

effect on acute motor speed and coordination. That is a problem when children are getting the drug, it does not seem to be a late effect, but it is an issue that if they are not doing that, when they are able to attend school, that we can wind up getting a delay during the course of treatment, and that is an issue we have to address.

As we are developing and looking at some of the anti-angiogenesis chemo, there are isolated reports, although we have not done a consistent study, that after enduring that chemotherapy, children may have very significant deficits in memory and attention processing speed, and we have seen a handful of those children. The question is does that recover after the medication is finished. We have not done that study yet.

We are considering methotrexate. We primarily use that in acute lymphoblastic leukemia. The questions there, it is an antifolate. Folate is essential to brain development, what impact will that have. We actually have a BCPA study that we are preparing to do in COG, getting ready to launch

this spring.

Then, of course, the platin-based medications related to hearing loss, and then there is a whole host of chemotherapy agents that we use in the treatment of children with brain tumors that we don't know the direct outcomes. We don't know what cyclophosphamide, CCNU, etoposide, and other new agents are going to do independently.

It is an important question as we move forward and begin to cut back on radiation, and in some of our trials even consider eliminating the use of radiation. We don't know whether there will be significant long-term effects with the chemotherapy protocols. These are questions that we are going to have to answer.

[Slide.]

The model that we are mostly working with is the treatment seems to have the greatest effect on the part of the brain that develops after treatment, and the parts of the brain that have developed before treatment seem to be relatively safe.

In the model that we have looked at that is similar to this, that what we see is early-on gross motor and language development is the primary area of development, followed by 3 to 6 years of age, fine motor skills, visual spatial skills, attention, visual memory, and things of that nature.

[Slide.]

When we look at this, what we have seen is that we can now, with not great certainty, but the model is being supported in a variety of different areas, we can predict to some degree what of those specific functional areas is likely to be affected based on the age at which the child is treated.

Our considerations in terms of looking at cognitive effects is when, in the course of normal development, does treatment occur that is disruptive, how complex is the mechanism or mechanisms involved in the treatment, and how old is the child at the time we look at late effects, because what we wind up seeing is that in children, part of our challenge in doing neuropsychological

testing with children is that our tests change.

Our tests change because children are developmentally changing, and so if we are going to look at something as simple as math, if we look at math in a 5-year-old, a child is able to do 1 plus 1 equals 2, and they can put the yellow blocks and the blue blocks and the orange blocks together.

We don't ask them to be able to tell us at what time two trains traveling to a midpoint starting at different points in time and traveling at different rates of speed would cross.

That is something that most of us around the table would have a little struggle with today, but at one point we probably could solve that problem. But it is a developmental issue where the brain, the connecting structures and the learning process provides the skills that are necessary to be successful, and we can't assess that skill or trigonometry until the child reaches the point where their brain development is there.

What we are anticipating, or the model that we are looking at now is that the process of

treatment of the child with brain tumor occurs at this point and the impact is out here, because of the developmental course and disruption. That is an important component for where we are at, and this is the type of falloff that we have using that same issue.

[Slide.]

What we typically see is when we have avoided radiation therapy in younger children, what the motor skills, unless there is a specific problem with the posterior fossa and long-term ataxia, the gross motor skills and language skills tend to stay relatively intact. But those abilities that develop at 4 to 6 years of age, primarily frontal cortex, are the ones that are impaired, and we wind up seeing children who have good language skills, but poor performance skills, and problems in some very specific areas.

[Slide.]

The predominant ones are slow processing speed, problems with attention, although typically not with hyperactivity, memory difficulties with

the primary problems not being memory for auditory information, but memory for visual processing and for sequences, some difficulties with fine motor coordination and speed that translates into handwriting primarily as a school task, planning organization and executive function difficulties that show up around age 11 or 12 when the brain is consolidating those particular skills, some visual-spatial motor problems, mathematics difficulties typically in the area of calculation, the ability that hits about 8 years of age when children are learning how to do their multiplication tables, which is primarily a memorization, a memory function for visual and novel information, although they do seem to understand how math works. So they understand how to do that train problem, but they can't get it right, because they can't do the basic calculations.

Similarly, in reading, it translates out to where children are able to do letter word identification. They are able to decode and read

out loud, but they don't comprehend what they are reading. So we wind up having not only a reading problem, but an across-the-board problem in their learning.

One of the other areas we are looking at is that children with brain tumors are the one group of children who really, in most of our studies looking at social functioning, wind up having difficulties.

It is not clear exactly what that is, but two of the neuropsychological components that we are concerned about are processing speed, because children don't process the telling a joke following the track of things as quickly as their peers do. So they tend to be observers from the outside, and not full social participants. There are also some indications that children may not be able to accurately decode social cues of emotion, both vocally and visually.

So, these are challenges that we have in terms of late effects for these children.

[Slide.]

This is just a cartoon showing the model that we are working on linking the types of treatment, the possible mechanisms, the impact on specific functions, and then the impact that it has on the kinds of things that children do every day in school that is directly associated with their quality of life.

[Slide.]

These are complicated issues, but we do have children with brain tumors that are surviving, so the other complication for us at this point is what do we do about them, because we don't have natural history.

No one at this point is comfortable saying well, let's just see what happens with the child over time, what is the intervention that we do for these issues.

Our biggest issue has been education. We have, over the course of our work in the cooperative trials, and POG, CCG, and now COG, adjusted primary therapy. The adjustments in the baby brain by delaying radiation therapy is one

such example.

There is work going on in a variety of places to try to identify neuroprotective medications that will protect the brain, the typically developing components of the brain, from the therapy that is necessary for treating the tumor.

There are a variety of other interventions like cognitive rehabilitation that unfortunately has not proven to be as successful as we had hoped it would; stimulant medications, but the FDA has put some Black Box warnings on some of the stimulant medications, and so our concerns related to children who may have received other therapies that increase the risk for cardiotoxicity, for instance, that may alter the way that the neurotransmitter works in a radiated brain.

These are questions that we have to be able to do careful studies as we move forward in this particular population.

Compensatory intervention in assisted technology is one of the other things that we are

working on. This is promising for children who have significant late effects, and one of the really exciting things that we are working on right now is being able to use the model about what specific learning problems, neuropsychological difficulties are likely to occur, at what ages, and then developing targeted interventions that will promote the development of that particular skill, not when it becomes a problem, but in anticipation that it might become a problem, perhaps starting as early as time of diagnosis.

So, I think where we are at with neurocognitive outcomes is that it is a lot more complicated in children because of the variety of mechanisms, unfortunately, the fact that there is a real challenge in being able to find access to the resources to be able to have the testing done that is specifically identified to carry out the studies and to be able to deal with the developmental changes that occur across time.

I will stop there.

DR. LINK: Thanks, Dan, and thanks to all

the speakers this morning for setting the stage for our discussions, certainly this afternoon of the questions.

So, unless there are any burning issues right now, what I suggest we do is take a 15-minute break, keeping in mind the questions that were posed that we were asked to give advice on.

So, the first thing we will do after the break is to address specific questions related to the presentations that you heard this morning, and that probably will take us up to the lunch break, and then this afternoon we will spend addressing the specific questions that we were asked to address.

So, if there are no burning issues now, how about a 15-minute break.

[Break.]

Questions to the Presenters

DR. LINK: As I indicated earlier, before lunch, and I think we have some time, so it doesn't have to end exactly at 12:00, but we would like to sort of go through questions for the presenters

that you heard this morning, but hopefully, some of your questions will be directed to the questions which we have been asked to answer.

Perhaps I will lead off this discussion in a general way and try to involve our FDA colleagues here to give us some help in terms of focus.

One of the problems that we see in pediatrics in general, and some of the presentations here are not going to make us feel better about it, is the diminishing number of patients and the increasing number of tumor categories depending on how we do.

It says you have heard that we just have more and more heterogeneity depending on how you look at it, and while this is good academically, it may not be good in terms of the kinds of things that we need to do for FDA, which is have robust studies with lots of patients.

So, I am wondering if you could help us, just to lead off after hearing Dr. Kieran's talk and some of the others in terms of additional stratifications based not only on histology, but

now molecular biology, different biology or different behaviors based on site, can we really help you in terms of that first question of risk stratification, are we getting to slice the baloney too thin, if you will.

DR. WEISS: I will start and then I will ask maybe my statistical colleagues here to comment, as well, and that is not necessarily a unique issue to pediatric oncology or pediatric brain tumor.

You know, the issues of stratification purposes for important prognostic factors comes up all the time, and I think the key thing is to be able to identify--and that is going to be a moving target as the science evolves--but to identify key prognostic factors, because too many strata will just make studies quite impossible to do.

The beauty of things like large, simple trials is that you don't really have to worry about those things, but that is really completely, you know, out of the question in most of the I think pediatric oncology settings.

But I think the idea of being able to identify a few of the key prognostic factors that can be agreed upon, at least for the purposes of a trial, and whether or not one can extrapolate certain information from tumor types based on certain biological similarities that might be something that could be feasible to do, but you are right, you have got a real problem with so much heterogeneity.

I mean that is what we struggle with even in trying to figure out what questions to ask, because outcome measures are going to be different and depending on what specific tumor types you are dealing with.

DR. SRIDHARA: I agree with Dr. Weiss. Also, you know, when there is so much heterogeneity, then, the differences you see, it has to be extremely large in order to see something significantly. Therefore, to stratify by some of these that you already know could be different is one thing.

Another point is by recognizing that you

have a different risk category or whatever, you could think of enrichment designs and things like that, where you start studying only in very high-risk patients rather than including everybody in the clinical trials, so that you have your endpoints sooner.

Sort of the analogy analysis, you do the studies in advanced diseases first, and then you move on to less advanced disease, so you could do the same kind of thing that, you know, you go to a high-risk group first and then move on to lesser risk group.

DR. BOYETT: There are two issues I think relative to stratification. If you know that something is prognostic, you stratify and you do in a randomized trial, you would do the stratification to ensure homogeneity of the patients randomized to the two arms.

But if you don't have a specific therapy for one of those stratas, then, it is not really a numbers issue that doesn't come into play.

DR. LINK: I am more concerned about the

molecular heterogeneity, that you may have a subset that would benefit from a therapy, like the Iressa trial, you know, but if you don't have 8,000 patients, and have a subset that is a 10 percent subset that is really sufficient patients to actually detect what may be a major impact on a very small subset.

We just don't have, even in the funnel going in, there are not that many patients, so you are not going to have very large subsets.

DR. BOYETT: Then, you have a numbers problem.

DR. PACKER: It is a follow-up to the statistical question and maybe something I just didn't understand from your presentation.

I guess it would be a two-part question. The first would be, given the numbers that we deal with in pediatric brain tumors, 3,000, 3,500 children diagnosed every year, multiple different subsets, and other than maybe low grade gliomas, not a great many in any one subset, can we ever really even consider doing a non-inferiority trial

for any condition given the numbers and the confidence levels you showed us.

If the answer is we can't ever do a true non-inferiority trial, what is the implication of not being able to do that trial, about getting drugs to the patients and evaluating, and then getting them appropriately released for pediatric patients, because one of the things we do battle with now increasingly for even the approved drugs is insurance approval to use the drug in the pediatric patient.

So, can we ever do it, and if we can't do it, what does that mean?

DR. SRIDHARA: I think that probably it is almost impossible to do a true non-inferiority study given the number of patients. More often than not, they are larger trials.

However, if you think that it is slightly superior, then, probably the sample sizes could be a little bit smaller than what you would normally see for a non-inferiority study.

Then, you have to think of what is your

hypothesis. If you truly believe that efficacywise, you are not really going to lose, then, you have to think about the toxicity. There has to be some gain in looking at this non-inferiority. Without a gain, why do you want another drug on the market?

So, there has to be something beneficial for the patient to consider any trial. Therefore, in the non-inferiority trial, we are saying the efficacy is about the same, but some of the advantage may be in either the way the drug is being given, IV versus oral, or whatever that you want to think about, are the toxicities better.

So, then, you have to be more specific about what is it that you are gaining from this, and maybe the hypothesis should be that. In that way, you may be able to get around this.

DR. WEISS: I was just maybe going to ask Ian Pollack or some of the other individuals that are very familiar with the COG studies--Dr. Pollack showed some slides that had outcomes in maybe they weren't true non-inferiority trials, and maybe they

were actually sequential as opposed to concurrent. But I thought they were actually concurrent, where he was able to show that in certain types of, for instance, medulloblastoma patients, one was able to show that the outcomes were as good, relatively good outcomes with reducing, for instance, the dose of radiation.

So, I am assuming those were maybe not the way we normally would like to think about it for these very, very large diseases in terms of non-inferiority, but they kind of got to where we wanted to go in terms of really assessing the outcome and being able to conclude that we had as good an effect with less toxicity. Is that overstating?

DR. POLLACK: No, I would agree. In fact, when the discussion about the non-inferiority trials started, I was thinking, now, what exactly is this. But in reality there are those type of studies and the ongoing study for standard risk medulloblastoma, which is randomizing, reducing the dose of radiation, reducing the volume of radiation

to the posterior fossa, and it has a set cutoff as to what would be considered an unacceptable decrease in event-free survival, 10 percent, and the study is powered to identify a 10 percent decrease in event-free survival with therapy reduction.

The flip side of that is that there are quality-of-life endpoints that are being included, because we would hope that, if there is a slight reduction in overall or event-free survival, there will be an improvement in functional outcome.

The same thing applies to the germinoma study, which is a randomization between standard radiation and chemotherapy plus reduced doses in volumes of radiation. The major endpoints in that are quality of life, as well as event-free survival, and there are event-free survival cutoffs that would be considered inferior and would cause the study to stop.

DR. LINK: They are not designed, though, as strictly non-inferiority trials. They are designed, you peg a basement low, which you would

be unhappy, and the confidence intervals around that, so it is not nearly as strictly designed as a non-inferiority trial.

DR. PACKER: Just to follow that up, that is a different design, and at this point we have been mainly looking at radiation being reduced. We have not been asking if we put in a different drug X, will it be available for patients, because it shows non-inferiority.

So, my question to the panel is will the design that we are using now for these other studies be adequate for the FDA's approach if we find drugs that we want to replace other drugs with.

DR. SRIDHARA: I think most of what you are saying is they are all single-arm studies, or you are comparing a radiation dose versus lower doses.

With the non-inferiority, as I was trying to impress, the comparator, the control arm has to be something where there is an established efficacy.

From what I am hearing, you doubt that, whether there is efficacy with just radiation, and then you are trying to combine with the chemotherapy.

DR. LINK: No, no.

DR. SRIDHARA: If that is not the case, and if you do have an established therapy, and if you can really estimate, then, there is a way to look at it. But, if you don't have an established therapy or if you are adding an experimental therapy to both arms, then, that becomes a problem.

DR. LINK: Jim, what can you suggest?

DR. BOYETT: I think one of the problems we are having here is that the standard of measure is different from that side of the table with the people around here.

The people that we are dealing with doing these trials are not trying to get approval from you guys to put a label on a drug. They are trying to convince themselves that they are helping these children. They are treating them and they are doing the best for them. They are reducing the

toxicity. They are not interested in getting a label as far as I can see it right now. That is a different perspective.

So, you have a much higher standard that you would hold someone to if they are trying to get you to label a drug for an indication, and that is not what is going on here, so the standard of comparison that is used is different.

As was said, that Mike said, the trials that Ian has talked about, they are definitely not non-inferiority trials.

DR. DAGHER: I just wanted to clarify something. If we created the impression that, in the adult oncology world, we rely heavily on non-inferiority studies, we certainly didn't intend to do that.

So, briefly, we really don't typically rely on them, period. So, it is a rare instance where we have used the classic, if you will, non-inferiority design that Raje, for example, presented. It is rare that we have used that even in the, quote, unquote, "adult oncology world" for

an approval.

Jim, the point you are bringing up is not just relevant for non-inferiority, it's a broader point, but I just wanted to clarify that so there is no misunderstanding about that.

DR. LINK: Well, you guys led off with it. Larry.

DR. KUN: Two issues. Number one, most of the trials that you have heard us talk about have either been Phase I trials, or we have not really been in the privileged position of looking at do we or do we not see improvement based upon adding drug X, which the adults have done with many, many more patients in a reasonably cohesive group of malignant gliomas.

The second thing, though, which may be tangential now, and I will only ask to come back to, and Karen and I have discussed this earlier, is that one of the things which is really most important to this group of people around the table is the availability of new drugs.

So, the issue about what is required

appropriately now in brain tumors for pediatric exclusivity shouldn't be ignored today, please, because that is critical to us in convincing companies, as we just did successfully this morning, to give us availability of an agent that looks promising in adults where they have no inclination to try it in kids absent your own support for that.

DR. LINK: Susan.

DR. BLANEY: Just as far as statistics and numbers, the other point I wanted to make on the trials that Ian presented today, some of those, even the numbers that we had to do, those randomized studies will become even smaller because now we are looking at different histologic subtypes of medulloblastoma, and as Mark said, now people are treating some of those as higher risk, whereas, before they were included in our average-risk studies.

So, we are starting to have orphans of orphans, if you can have that, and our numbers are getting smaller and smaller as we learn more about

the biology of these diseases.

DR. LINK: Could I just, at the risk of sounding stupid to the statisticians, one of the underpinnings of a non-inferiority trial is that the C versus the placebo was actually not such a huge effect, like you were talking about 20 percent improvement, or risk reduction.

But in many of our trials, like in medulloblastoma, we have an enormous difference in risk reduction compared to placebo. So, does that affect the numbers?

Let's say you wanted to take an 80 percent or 75 percent of the contribution of the control, when the contribution of the control is huge as in medulloblastoma, because that is a group of children where we are curing them, and it would be a group of children where we would want to introduce a toxicity-reducing agent, for example. But we want to be certain, as certain as you can from a statistical point of view, that we haven't compromised tumor control.

So, that would be a model where we would

be interested, but where the control actually has a huge impact, what kind of numbers would we need to go to?

DR. SRIDHARA: Definitely when the magnitude of the effect is much larger, the sample sizes go down. But it also depends on, you know, when you have a huge effect, then, you want to retain most of it.

So, you know, you may not say 50 percent retention. In that case, you may say you want to retain 75 percent retention, but still, when you have a larger effect, the studies would be smaller.

Yes, if you have more patients, and the effect is much larger there, and yes, that would be a place to do a non-inferiority trial.

DR. LINK: When you say smaller, I mean how many zeros? Like smaller like we could do it, or smaller like it is still out of range for us.

DR. SRIDHARA: It depends on, you know, as I said, what percent retention that you want, you know, how much of the defect you really want to retain.

For example, if you just want to be better than placebo, period, then, you don't have to leave in anything, and, if you say 25 percent retention, that would be a much smaller sample size versus a 50 percent versus a 75 percent.

So, it will have to be really worked out, and again it also depends on the endpoint. Typically, if it's a response rate that we are looking at, then, the sample sizes are much smaller compared to a time-to-event endpoint.

DR. LINK: I am trying to anticipate the kind of studies that Roger would be talking about, or Dan Armstrong would be talking about, something where we know we can cure the patients, and we know we have a huge impact, but we are trying to reduce the later thing.

Malcolm.

DR. SMITH: I want to clarify something about the studies we are doing now, and with deference to the statisticians in the room, on the study that Ian described with our standard risk medulloblastoma now--I mean that is what we used to

call an equivalent study or non-inferiority study, but that is what it is.

You are comparing a standard therapy, you are trying to reduce the dose of radiation. You are inflating the Type 1 error, and you are raising the power so that you are favoring your ability to detect if there is a true difference, in our case of 10 percent, from the standard treatment to the experimental treatment that reduces therapy.

So, we are doing those kind of--you know, this is the design that we are using now in the medulloblastoma study. What limits us is just that, you know, we are enrolling I think the target is 400 patients, and 400 patients in large measure is picked because that is five years of enrollment. It is the best we can do.

You go much longer than that, and the question becomes uninteresting and it is really the best we could do. Conceptually, it is really no different than if we use standard dose radiation and we added a drug to it to reduce toxicity, so we are doing these kind of studies now.

We are using an equivalence or non-inferiority type design where there is a standard treatment, and we are monitoring for decrements of a specified amount with an inflated alpha and with an increased power.

We are just limited by the number of patients that we have to do these studies with the kind of robustness that we would all like to be able to do them with.

Really, probably standard-risk medullo is one of the--there are not a lot of places where we can do the study, standard-risk medullo may be our best shot at it.

Jim, or I would appreciate feedback from the other statisticians because that is the design we are using now for our standard risk, and I think if we were to add a drug to radiation to reduce toxicity, we would use a very similar design.

DR. BOYETT: Malcolm, you can call it equivalence, but if you actually take the two approaches, the quote, unquote "non-inferiority, and the way that we are designing these, they

really are not the same.

The non-inferiority, if you do it truly that way, it is going to cost you more patients. I don't disagree with what COG is doing, I think that is the right approach, because we aren't trying to get labeling. You know, you are trying to do the best you can for the patients and continue to have good results and reduce toxicity.

So, I am not criticizing those particular designs. I have designed some of those myself.

DR. SMITH: I guess I would need to know what the difference is with non-inferiority, you know, in terms of I mean it is just we would do a larger study to detect a smaller difference if we could. It is just we don't have enough patients to do that within less than five-year period.

I guess it is unclear to me exactly how the design differs. It is taking a lot of patients already, and how it differs other than that if we could, we would target a smaller difference to be more confident that we are not reducing outcome.

DR. SRIDHARA: In other words, that is the

risk you are taking. So you are willing to give up a certain amount of efficacy which you think is okay, and that is the fixed margin approach that we don't normally go with it, because we want to make sure.

No study comes, you know--there is no exact that this is the true effect. We don't know, and, usually, there is some variability.

In the approach that you are taking, you are saying there is no variability, this is, in fact, the truth and we are going with this, and if there is a 10 percent decrement, that is what it is.

By increasing the Type 1 error rate, you are increasing your false positive rate, so at the end of the study, you know, you have a result, but is it false positive is the question.

DR. PACKER: This is, I think, not just hypothetical, because it could be that the next set of studies we do for the average-risk medulloblastoma will not be a reduction in radiotherapy but may be the introduction of a

radioprotective agent and the reason we will get the radioprotective agent will be because a company wants it labeled.

One of the things that we are going to have to work out as a community is given our numbers, what we might accept as clinicians may not be what the FDA accepts, and that will be either blocking the study or doing a study that will never go anywhere because we will never accrue the numbers that is being requested.

I think that is why I am raising it, that if non-inferiority is going to be the standard for labeling of a drug, in the future that may limit what we do versus the way we are doing it now.

Those people want to give us those radioprotective drugs, the companies, because they want it labeled for that, and that is what my concern is hearing the conversation.

DR. DAGHER: I would ask, maybe it's naive, but if, you mentioned, you know that the main interest is in actually showing an advantage in the toxicity profile--and this is just an

question, an individual question, it is not reflecting the FDA position or anything else--why wouldn't one actually design a superiority trial looking at that endpoint as the primary endpoint and then looking at the standard efficacy endpoints that you just want to maintain as a secondary.

I don't know how, maybe we have done that already in the past, you know, we have contemplated that. This is just a general question.

DR. LINK: The time to get that endpoint--remember these are cured patients, and you are looking at school performance nine years later, and that would be the disincentive.

I think that one of the ways we design the studies is we are really designing our studies as anti--to prove that they are better. You take a study and you take your standard, and that becomes your experimental arm. You say, you know, what you normally would have said is, is an additional dose of radiation 10 percent superior, and you just take the design and flip it.

I think that that is, in fact, what we are

doing academically, which is why it is different from a non-inferiority design. By the way, there was a very nice article in the JCO a couple of months ago about non-inferiority designs.

I only understood the first couple of paragraphs, but it basically outlines all this and why they are different, and you understand that they really are very different.

I think the question that a lot of us on this side of the table are asking is would it be acceptable, if we could incentivize a company to sort of do this kind of study of a radioprotectant, would they accept the kind of ways that we do studies that make it acceptable to us, and we know that we have made progress, that we can reduce the dose of radiation, we are happy with it and we are willing to tell our patients that.

We accept it as a community of oncologists, will it be acceptable to the FDA to then go and allow it to be labeled based on this not as good kind of statistical design.

DR. WEISS: Believe it or not, there is a

fair amount of flexibility at the agency, and I think that all of us who deal with rare diseases and serious life-threatening diseases just realize that while the algorithms that are used in like cardiovascular diseases or hypertensives or whatever have a lot of attractiveness, that is just not the reality.

You can't do those kinds of studies, you can't have those kinds of numbers, and you can't have that kind of--all the things you can do with factorial designs, et cetera.

So, usually the process would be--and I think this is very good to get this out in the open, that if a particular manufacturer is really interested in developing something for a pediatric brain tumor population, and it has got a specific hypothesis or potential indication in mind, they, along with the appropriate people, whoever they would like to bring from the NCI or COG, would be meeting with us, with the agency, usually at an end of Phase II meeting, to really discuss the suitability of that particular design.

In fact, there are other mechanisms at the agency, like special protocol assessments where they would actually submit in detail the protocol, usually including things like case report forms, and we would specifically enter into an agreement about whether or not that study, should it prove to be successful, would result in basically a labeling.

So, there are very specific mechanisms. I do think that those of us at this side of the table are very realistic about what are the limitations in some of these types of diseases.

There might be implications, we might say a design like this might be able to give you this kind of indication, or the labeling might not be able to say much about the comparator arm, but we would figure out how we could get to where we all want to be at the end of the day, I would think.

DR. ARMSTRONG: I guess one of the questions that is sort of the elephant in the room as we think moving forward, within the next year we are going to see in a variety of diseases, somebody

who is going to do a microarray and put together a polymorphism schema that is going to be very targeted to select groups, and we are going to have some folks who are going to be doing pharmacogenomics on it.

The move toward targeted therapies for rare groups is happening, it is happening very rapidly. I guess one of the questions that fits into this is do we have the kind of cross-communication between our statistical process in COG, the FDA, and the development of the kind of mechanisms that are--we are going to have smaller groups as we develop individualized approaches to therapy, and it just seems like in a lot of areas, it is happening very quickly.

Can we put that on the table and think about how that is going to move forward, because I suspect that will be an issue for us as we treat pediatric brain tumors, you know, the advance of therapies in genomics.

DR. WEISS: There is certainly a huge effort, in fact, we were initially going to have

some discussions at this meeting on area of what is called "critical path" at the agency.

That is going to have to be postponed to another meeting, actually to include representatives, not only for the pediatric oncology area, but in the adult oncology community, because the whole idea in critical path is to actually look at specific targets, biomarkers, biomarker qualification.

There is a large effort at the FDA with individuals that have very specific expertise and interest in the pharmacogenomics and pharmacogenetics, biomarker qualifications.

If you have got a very specific mechanism and a very targeted therapy, and I know like Rick likes to talk about the Gleevec story, for instance, that you may not need-I mean if it's something as exquisitely sensitive to the therapy, and the rationale is there, you may not need that many patients to show the effect that you want to see.

I agree it is a rapidly evolving field,

and what ends up happening--I mean there will be questions down the road about looking at biomarkers and validation. I think we are not at that point yet, but we certainly are at the point where we can maybe thinking about rational selective individualized therapies based on molecular mechanisms.

DR. PAZDUR: I view this really as a positive aspect, the ability to identify and enrich a population, and I think this is really going to be the kind of savior, in a sense, as this field moves forward. But I think it requires some careful planning.

First of all, one has to start developing these targets. We can't just have mythical targets that we think that the drugs works through, because that has been present in oncology since we began this field, that drug X works on this enzyme, et cetera. But really a targeted drug, for it to be clinically useful, has to have a target that can be measured, so we can identify a subpopulation that would work.

This requires some additional work with usually a device manufacturer to set up the test kit that one would need as one moves forward. But a true targeted therapy is not a targeted therapy clinically unless one has a target to identify and enrich that population.

Frequently, this field has not been developed well even in adult oncology with a lot of so-called targeted therapies, not really developing the target well, for example, not exploring it in a target-negative population, et cetera.

But as Karen pointed out, and as Raje did, this whole area of enrichment is what this whole target approach is. If you have a drug that has a 10 percent response rate, and that is all you have, that means 90 percent of the people are being treated and exposed potentially to Grade 3 or 4 toxicity, and the risk-benefit of that picture in most people's mind would be quite negative.

Whereas, if you have a drug in a population where you have it targeted, and that response rate is 60 percent, one would be much more

willing to license that drug.

This whole issue of targeted therapy is one that is being grappled with in adult oncology, and I think it is part of the general picture in drug development.

DR. SWISHER: There are a lot of things that I have interest from the patient perspective. But. on standard-risk medulloblastoma and small molecule inhibitors, if you look at the sonic hedgehog pathway, I think somebody here who knows more than me, it is about 10 percent have the sonic hedgehog pathway, give or take? Maybe 30, okay 30.

That is 180 if you use 600 as the "n" per year, and you use that as one group, how long this is going to take to find that group that might respond to a sonic hedgehog pathway, small molecule inhibitor versus looking at another risk stratification like ERBB-2 and trying to incorporate that, it looks like we are going to very, very small numbers even in standard-risk medulloblastoma, which is for pediatric brain tumors one of the larger groups.

How do you try to look at that?

DR. PAZDUR: If you truly have an effective therapy, you would need smaller numbers of patients. Here again I can't comment on the specifics because I am not a neuro-oncologist, knowing the numbers of patients here, but in general, when you are dealing with a therapy that is markedly more effective in a disease, you know, you need smaller numbers of patients, and we generally would be looking at smaller trials.

A perfect example of this in adult oncology would be GI stromal tumors. It would be said years ago that we would never have been able to do these trials. However, with internationalization of trials, trials networks, looking at accrual, not only in the U.S., but also in Europe, actually, randomized trials were done in a disease that most people thought single-arm studies would only be possible.

So, here again, I can't answer your specifics as far as the disease, but in general, when you have greater efficacy, the regulatory

decision is so much more easier for us to make.

It is much more easy for me to sign that letter when we are dealing with a response rate of 70 or 80 percent even in a small number of patients rather than a 10 percent drug where you might have thousands of patients in it. That risk-benefit relationship is so much more easy for us to deal with.

DR. KIERAN: I guess the concern about the 10 percent versus 70 percent response rate is that it is by identifying the 10 percent that you can isolate that population and focus on it, so that you can then, in working just with that population, turn it into a trial in which you have an opportunity to see the 70 percent.

The other concern is that unlike the adult trials in which if you accrue a couple hundred patients, and you see that 10 percent that interests you, when a pediatric trial made up of 50 patients, you don't see the 10 percent because they are not properly designed that way, which means you never know which population to focus on.

I think those are the things we are going to have to overcome, particularly with respect to some of the new biologic therapies, and how to move forward.

DR. LINK: I think as Rick pointed out, if you do your homework first, you have a better chance of deciding, you know, finding out who that 10 percent is going to be, and you may be able to do the trial in 50 patients.

DR. KIERAN: But it sometimes requires an a priori knowledge, and the lung cancer trial with Iressa was a good example. They didn't know until after the fact.

DR. LINK: Exactly. We are not going to be able to do it that way.

DR. KIERAN: Right, exactly.

DR. PACKER: But to go directly back to your point in stromal tumors, you were working off a survival rate that was quite poor. When we were talking about the sonic hedgehog pathway, we are coming from a survival rate that sits around 80 percent overall.

So, now you are trying to put a safer therapy, a more targeted therapy that may cure 90 percent. You are still going to need large numbers even if you are able to identify that group out. That is going to be one of the challenges.

The other thing that I am wondering about as we move along with this, and I would like to know how you do this. We have done very well in the pediatric brain tumor community of continuing to stratify patients, but maybe the paradigm to get these drugs in is a different stratification.

To use your assay for every kind of pediatric brain tumor that has a specific amplification of EGFR independent of whether it's medulloblastoma, high-grade glioma, and ependymoma, and utilize that targeted therapy just for that across different tumor types, is that a reasonable approach as we look at targeted therapy?

DR. PAZDUR: Yes. We are not hung up on the classical histological definitions of diseases. But here again, I think that requires a scientific underpinning that is accepted by the greater

scientific community. It just can't be one trial that you just put everybody in, there has to be a buy-in that this is the way to go.

There is nothing in the regulations that govern the FDA that says that we have to approve a drug in breast cancer or colon cancer or whatever.

This is highly problematic and it goes back and I think has to do a lot with how we develop drugs in the United States and a high degree of collaboration that is only going to have to occur if this is going to be successful.

Let me emphasize drug companies are in the business of developing drugs. They are not in the business of developing diseases, and what you really talking about is a paradigm shift away from a millennium basically of experience with histological diagnosis, moving to molecular diagnosis.

This is really going to have to require the cooperation of the government, particularly the NCI moving this forward, as well as the FDA accepting it, as well as the practicing physicians,

and also be result driven.

Many times we are talking about these markers and these effects independent upon the results that one gets, and here again, big effects are easy to demonstrate that this truly is a real finding.

DR. DAGHER: I wanted to clarify something about the GIST picture just to illustrate the point further, I think, that Rick was trying to make. In that case, many people know, but we will just kind of rephrase that.

At the time of the approval for GIST, we weren't waiting for any progression-free survival results for that matter. We based the approval based on a roughly 40 percent response rate observed in a Phase II study that included a little bit under 150, it was 147 patients ultimately.

It was a randomized Phase II, it was just comparing two dose levels, but we essentially viewed it as pooling those two arms together and saying in these patients--it was those patients who had unresectable or progressive disease, and in

those patients, we know that even with radiation or anthracyclines, the response rate is less than 5 percent.

So, in that case, I think to amplify what Rick was saying, when you have a 40 percent response rate of pretty impressive duration, that was then followed up further, there wasn't much doubt, you know, do we need a randomized study.

So, even though there were a couple of other randomized trials that were in planning or further initiated, one in the U.S. and one in Europe, we weren't waiting for those results to make the decision on the approval.

So, just to kind of illustrate, 147 patients versus actually the other two randomized trials, each which enrolled I think close to several hundred each subsequently, but we weren't waiting for those results to decide on the benefit.

DR. LINK: The problem with using a pathway as your target is it is still contextual, so you may see all the responses in medulloblastoma even though the same pathway may be in other

tumors, but it is not the only pathway is active, so you still may have a problem with numbers.

DR. WARREN: So, where are you going to put the drugs, the targeted drugs that actually hit their target, but they don't result in improved clinical response or any clinical benefit, but you can prove that they hit their target? Is there any role for like a sub-Phase II study where you can prove efficacy by enzyme inhibition, but no clinical benefit, and then move on to a clinical benefit trial with combination trials?

DR. WEISS: The end result would be you would have to ultimately show that the drug, either alone or in combination, has some benefit, and if you have got some good studies that have some provocative results in an early development phase.

You know, a lot of times Phase II is your time to explore a lot of issues with respect to potential appropriate markers or potential outcomes.

There might be appropriate surrogates and is a good impetus to take to other trials. That

can be done, it is just I think--

DR. PAZDUR: I think she is talking about--you mean approving a drug just on the basis of--

DR. WARREN: I am afraid what happens is, if you have a negative Phase II trial, meaning it doesn't show clinical benefit, then, that drug is no longer developed in the pediatric brain tumor setting.

DR. WEISS: I mean unless there is a rationale for using it in combination. There are plenty of cases where, you know, old drugs were at one time thought to be just dead, and then they got resurrected for whatever reason, there is a good rationale for combination or a new disease that came along. I think that is the AZT story from many years ago.

But you would have to make sure that there was an appropriate rationale for actually why you would want to use it, if some of the earlier studies--we found there are drugs where something maybe didn't maybe work in advanced stage disease,

initially, the development stopped, and then there was some reason to put it into early stage disease or vice versa. There are a number of stories like that.

Certainly that is feasible. You don't want to kill a drug that might have some appropriate place in the armamentarium, but it is a question of sort of finding where that niche would fall.

DR. PAZDUR: But here again, I think that is more of a development issue of the people that are doing the investigation here, but from a statutory basis, for a drug to be approved in the United States--and this is not something that we could just change here, is that there has to be a demonstration of clinical benefit for a standard approval of a drug.

DR. WARREN: Alone.

DR. PAZDUR: It has to be isolated. Let me give you an example of where this might work.

For example, say when leucovorin with 5-FU was being developed, obviously, leucovorin itself

has no anti-tumor activity whatsoever. However, when it was combined with 5-FU, there was an enhancement of that activity.

So, the study that led to the approval of that drug was 5-FU versus 5-FU plus leucovorin. We didn't demand that you do a leucovorin arm alone in metastatic colon carcinoma, because that would have been ridiculous. Everybody knows that this is a vitamin, et cetera, or would not have any activity, but we have to have some assurance, because we are licensing a drug that will be marketed, that under the statutes that govern the FDA, that there is for a standard approval clinical benefit, or for accelerated approval, an effect on a surrogate endpoint that reasonably likely predicts clinical benefit.

DR. WEISS: And I would just say that on some kind of biological or pathway, we are not yet there yet in terms of that being a reasonable surrogate to predict clinical benefit.

It might be reasonable to further study it in some other context, but we are not at that point

where we have accepted those, at least in the oncology setting, as appropriate for an accelerated approval.

That was just a comment, and there are others in the room that know a little bit more about this history, including especially Dr. Gootenberg, that the approval of the asparaginase, particularly the PEG-asparaginase Oncospar was based, not so much really on the clinical outcomes, but on looking at a pharmacodynamic effect basically, the asparagine depletion, because it would be very, very difficult, particularly when we are looking at that drug in the newly diagnosed setting to be able to show a difference in effect--actually, Malcolm could comment on that, as well, better than I could--to show you would need large--it's again the whole idea of non-inferiority design.

If you wanted to show that PEG asparaginase had an extremely important effect on patient care because of the decrease in the number of injections, and you wanted to have some comfort

level in the fact that you weren't giving up really any efficacy, but, in fact, it would take large numbers of patients and a very long time to basically do the traditional non-inferiority study even in acute leukemia, because the outcomes are so good.

But we were able to show that you had the effect that you needed, the pharmacodynamic effect, and that also might be, not just the molecular hitting the molecular target, but, in fact, looking at PK/PD correlates as another way to consider rational drug development.

DR. PAZDUR: Basically, we did not ask for a survival study to be done there, but that was again based on a thorough understanding of the drug. Here again, how many times do we have that thorough of an understanding? It required a lot o precedent work to really come to that conclusion. That developed over decades, let's face it.

DR. WEISS: It's a different topic, but maybe it's a good thing as a break before either the public hearing or before lunch, I am not sure

what is next on the agenda.

When Dr. Armstrong mentioned the developing field of pharmacogenomics and looking at targets, we were talking about the efficacy side of things.

I know that Dr. Armstrong in particular has got an interest in this area, but there is also a big interest, not only at the agency I am sure, but by academicians and companies, in looking at pharmacogenomic markers for the adverse events and trying to predict--and maybe we will get into some more in the discussions.

I don't know if now is the time, or you want to save this until after lunch, but trying to also look at various types of patient factors that might help predict who is more likely to, for instance, experience some significant neurologic sequelae, who might benefit from some types of intervention.

That is just another area that it's even probably further behind I think than the efficacy side, and it is also an area that I think it's just

important to pay attention to particularly in this particular field.

DR. ARMSTRONG: I think that would be a very good topic for an awful lot of discussion in the afternoon. Clearly, the questions, when we historically look at neurocognitive outcomes as an adverse event of treatment, historically, what we have looked at is IQ.

As I presented, it really is very specific kind of functions on the developmental model. There are very likely those kinds of targeted questions at a polymorphism level. We have not mapped out, even forget the genomic component, we have really not mapped out the biochemistry, the metabolic activities, the other biologic mechanisms of how these kinds of things occur.

Being able to think about that as we look at the development of new drugs and new treatment approaches, understanding those mechanisms may and would likely lead us to the point where we can alter the therapy in a way that we get maximum survival. But yet we minimize those late effects

or develop alternative and complementary interventions, either behavioral or with new drugs that actually facilitate the developmental process and salvage things down the road.

I think we have got to be thinking in a much more complex manner about the adverse events and thinking about cross-medication interactions and contributions down the road.

So, it is the future science, but it may be right around the corner.

DR. LINK: If we don't have other comments for the speakers right now, we do have one public speaker.

Open Public Hearing

MS. CLIFFORD: Ms. Weiner, if you could take the podium.

DR. LINK: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing session of the advisory committee meeting, FDA believes that it is

important to understand the context of an individual's presentation.

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If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

I don't think anything will preclude Susan from speaking.

DR. WEINER: It is both fortunate and

unfortunate in some sense that I have no conflict to state.

I am Susan Weiner. I have known lots of the people in this room for a long time. This year I serve as the co-chair of the North American Brain Tumor Coalition, the vice president of the New York-based Children's Brain Tumor Foundation. I am also the family patient representative on the Pediatric Brain Tumor Consortium.

I am the mother of Adam Weiner, who was diagnosed in infancy with a brain tumor and died of his disease 13 years later.

Today's panel eloquently described the complexities of brain tumor research, so it is really unnecessary for me to restate the dire needs of children and families for more effective and less damaging brain tumor therapies.

All of us I am certain agree that the current slow pace of development of new therapies for these diseases cannot continue.

As physicians, nurses, researchers and parents, we have seen too many of our children die

and watched the progressive effects of treatments on survivor's thinking, speaking, learning, and ability to live independently. Cure in pediatric brain tumors means survival with a compromised life.

If there are to be more rapid improvements in treating our children, it is essential that FDA personnel, academic pediatric oncologists, NCI, those in industry and families work more closely together to solve the complex issues being discussed here today on an ongoing basis. I would like to mention three strategies that may help accomplish this.

First, those at FDA who review plans and studies of pediatric brain tumor therapies and those who make regulatory policy, either explicitly or implicitly, that affect pediatric brain tumor patients need to be consistently mindful of the special needs, constraints, and resources in pediatric oncology research.

Too often advocates hear from the academic community and from industry of inconsistencies in

the judgment of FDA personnel and the unnecessary delays that result in the process of developing pediatric oncology therapies.

Second, collaboration among FDA, the pediatric oncology community, and advocates--as Dr. Pazdur said earlier, having left us out, though, please don't leave us out--is vital to shaping novel trial designs, endpoints, and imaging techniques, so that these tools can be meaningful for pediatric brain tumor research.

The strict application of regulations in pediatric brain tumor research is just unrealistic. Given that these diseases are so severe, and the numbers are so small, decisions about research must conserve patient numbers and patient data.

Our children with brain tumors need scientifically sound treatment options in the shortest possible time and cannot wait the years it takes to conduct relatively large randomized clinical trials.

The use of historical controls whenever possible is one such example. The use of Phase II

data for drug approval is a second instance, and the use of imaging techniques and parameters for surrogate endpoints is an additional important example.

For children with brain tumors, drug efficacy cannot be decoupled from their developmental course or quality of life. We simply must do better.

My last point concerns the pediatric exclusivity incentive. Applications of this law depend on definitions of equivalence between pediatric and adult disease, questions of substantive scientific debate, as we have heard this morning.

Further, the six-month incentive only applies at the end of a drug's patent life and therefore is a weak incentive in getting the newest agents including pre-approved drugs into trials for children with cancer.

The Best Pharmaceuticals for Children Act is up for reauthorization in 2007. In its current form, FDA, academic pediatric oncology researchers

must use this incentive to prioritize written requests so that the incentive can be used to make greater strides in treatments for children with brain tumors and other cancers rather than small increments in knowledge about currently imperfect therapies.

We will be working to have the Best Pharmaceuticals for Children Act reauthorized in the new Congress, and to revitalize it for pediatric oncology drug development insofar as we can try. We will also seek to have it applied to biologicals, which it currently does not do.

Parents' willingness to enroll their children in clinical studies has been essential to the improvements we have seen in survival rates in many pediatric malignancies. In pediatric brain tumor trials, our children have been less fortunate.

I am grateful to the FDA and to the Pediatric Subcommittee of ODAC for openly discussing some of the barriers to more rapid development of brain tumor therapies.

Today's meeting is a clear example of how important this subcommittee is and how it can provide a forum for analyses of the complex issues inherent in advancing treatment for children with cancer.

Today's discussion and others that have taken place with NCI researchers and patient advocates need wider dissemination within FDA and in the pediatric oncology community in order to promote more efficient and consistent approaches to brain tumor therapy development.

In this time of reduced federal resources for cancer research, we need to take advantage of every opportunity to accelerate new therapy development.

Families and patients urge and expect FDA, industry, NCI, and the academic community to work more closely together, and we continue as always to be willing to do whatever it may take to bring the best therapeutic options forward for our children.

Thank you for the opportunity to speak today.

MS. CLIFFORD: Thank you, Dr. Weiner.

DR. LINK: We will now adjourn for lunch. Although the schedule says 12:00 to 2:00, that was really a typo, so it is going to be more like 1:15 that we would like to return here.

You will hear the possibilities for your lunch choices now from Johanna, but over lunch I urge you to be thinking about, maybe take it along with you and read the questions again. It is pretty dense, but read it because that is what we are supposed to discuss this afternoon and we would like a spirited discussion.

MS. CLIFFORD: But don't discuss the questions at lunch. Thank you.

(Whereupon, at 12:00 Noon, the proceedings were recessed, to be resumed at 1:15 p.m.)

A F T E R N O O N P R O C E E D I N G S

[1:15 p.m.]

Questions to the Pediatric Oncology Subcommittee and Discussion

DR. LINK: I am going to start this afternoon and we are going to try to address the questions that were posed. I hope all of you have read them, but let me just sort of make it clear what they are.

Question 1. This is a heterogeneous group of tumors whose biology, clinical manifestations, treatment and outcome differ from one another and from brain tumors in adults. Treatment decisions are based in part on risk assignment models, low, intermediate, and high risk.

For example, patients with low-risk characteristics receive therapy aimed at maintaining excellent survival while decreasing toxicity. Risk models may also be useful for regulatory purposes, e.g., in determining optimal endpoints and other study design features for new agents with the ultimate goal of market approval

for the treatment of pediatric patients with brain tumors.

So, the first questions that we are asked are to discuss the value and/or pitfalls of categorizing pediatric brain tumors based on risk strata as a first step to defining appropriate outcomes for use in regulatory decisions.

Secondly, if it is appropriate to develop categories, please suggest: (a) categories and (b) the criteria for such categories. The criteria should include, for example, histopathologic characteristics and grade alone or in conjunction with other demographic and disease factors.

I will open the discussion.

DR. WEISS: Maybe it doesn't need much clarification, but in the past when we talked about the various disease-specific workshops, there wasn't probably as much heterogeneity as you are talking about with this particular situation, and when we get to the issue of Question 2, which is really the meat of the discussion about what are appropriate endpoints, obviously, one could say,

well, overall survival is what you need.

Well, it may be appropriate in one setting, such as high-grade tumors, but maybe not appropriate in some other settings, so we thought we first had to figure out what are sort of these big categories, if that is even feasible to do before we could actually start getting some advice from you on what are appropriate endpoints.

I hope that is a doable task.

DR. LINK: Who wants to take a first crack at this?

DR. BLANEY: I would say just on general terms that there are two basic categories, and those are our high-risk patients--for example, our brain stem gliomas or other high-grade gliomas--and a subset of infants and other tumors, such as atypical teratoid rhabdoid tumors, which are definitely high risk.

In general, they go across very different histologies, but in those cases, something like survival, whether it be progression-free or overall, would definitely be an endpoint that we

would look at, because we don't have therapies that really impact in any way survival for those patients.

But then as a lot of our discussion was this morning, we do have treatments. For example, our most common tumor that we see is medulloblastoma where we are effective in having 80 percent of the children survive for a meaningful period of time. But that comes at a very high cost and so what we really need to do for those patients is have different study endpoints to improve and lessen the morbidity of therapy.

But as was said this morning, even within that subset, and as we learn more about pharmacogenetics, that big subgroup of patients is going to be further divided and subdivided.

DR. LINK: Where would you put the infants?

DR. BLANEY: Well, even within infants, if you look at medulloblastoma now in the literature, there are probably different categories within medulloblastoma for infants. I mean overall I

think the survival is more, but I would consider them high risk.

DR. PACKER: One of the difficulties in addressing Question 1, it is sort of a two-edged sword. Much of our progress in helping children with brain tumors and helping families has been our ability to start separating them into reasonable biologic subgroupings, so we could tell families who might respond to therapy, who might not respond to therapy, who may survive, who we are really worried about late effects about, and who we are really talking about more short-term toxicities, and that may be one of the major problems we have in working with the regulatory organizations in getting new drugs to our patients, because as clinicians, we want to be very exact.

We want to know exactly what we are dealing with and want to let families know exactly what we are dealing with, and tailor therapy as closely as we can, so we don't overtreat or undertreat.

At the same time, from all the

conversations we have had to date, that seems to be a major problem of getting a new drug to market unless we have a disease that is so terrible that, in a short window type of study, we could show efficacy, so we can move it quickly to the children.

So, yes, maybe for brain stem gliomas, it won't be hard to bring a drug if we found the right assay and the right pathway, and the right drug to hit the right target, but for a lot of the other things that are sitting at 50, 60, 70, 80 percent, 90 percent survival rates, where we have a lot of toxicities, it is going to be very difficult to make the leap without maybe a new way of thinking about how we are going to work together.

So, that is my problem with how we are going to approach this question. I don't want to give up everything I have learned in 20 years just to get a drug to a patient. There has got to be a way to balance that out

DR. LINK: Other comments? Susan.

DR. BLANEY: I just want to say, and I

agree with Roger because another big subgroup of the patients we see, which we haven't even talked about today, is our low-grade glioma patients, and there is morbidity associated with that therapy.

Lots of those patients aren't even treated in the clinical trial setting, but we have to have a mechanism as we do clinical trials and try to improve on that treatment, to perhaps even retrospectively then come forward and garner approval for an agent or an intervention.

DR. LINK: It sounds like when we are talking about risk strata in terms of who we are willing to put on early phase clinical trials, but I am not sure that that is helping in terms of how to get the drugs.

DR. WEISS: What we were primarily looking for--I mean, obviously, there is lots of discussion that could be had, but what we were focusing on, similar to other endpoints development, is we are really talking about late stage Phase III trials, things that would establish efficacy for the purposes.

Again, I know it is a little bit of a different perspective from the community versus the FDA, but for the purposes of actually getting an indication and getting labeling.

What we wanted to say is this potential group of diseases, the strategy might be again towards the toxicity reduction or, in these diseases where progression-free survival is like 50 percent, we still really need to have therapies that will actually improve that particular outcome.

That was the genesis of trying to develop this particular question.

DR. KUN: In the context of that type of assay, if you will, Karen, I am not sure. Maybe it would be worthwhile polling the group if there are any agents that even might be potentially available within the next, let's say, two-year time frame, that would go into a Phase III study either of efficacy or of ameliorating toxicity, because I am not sure we have such agents available.

There might be endpoints. Is that something we are not allowed to discuss?

DR. PAZDUR: When this committee was set up, it was not to discuss specific agents, and that needs clearance and a whole different level of scrutiny of what goes on, so I would not get into specific drug topics.

DR. PACKER: Can I try to ask the question maybe a little bit differently? Let's say that for a very common tumor, the low-grade glioma, we have significant biologic data, and then we would have to work with everyone to agree that it is significant biologic data, that one or two critical pathways are active in that tumor fairly uniformly; that we have therapy right now that can effectively treat that tumor, but with significant morbidity, maybe not horrendous morbidity, but significant morbidity.

What the question to the group would be that, let's say, we want to introduce early in the course of illness, therapy with one or two classes of biologic agents that hit these targets. It is unlikely that we are going to be able to show better efficacy than what we have already done.

It is also going to be potentially a study that is going to take a long time to do, yet, it is a study that we all want to do.

So, the question is that if we identify a biologic subgroup and it isn't one of children who die all the time, how do we move that along? How do we combine those two biologic agents quickly to make a difference in the therapy of those children.

I could take that more specifically and name the agents, but I am not--but let's just say we have the pathways and we have a way to do it, and we even could get tissue to prove that those, in that individual patient, in an assay that those pathways are likely to be present.

DR. WEISS: I think that I would turn it around and want to know from the experts, and if you pick something like a low-grade glioma--I mean it is sort of hard I guess to do in the abstract, but if you pick the specific type low-grade glioma, the important question would be what is it that you are trying to affect, what is it that is the outcome of interest that this new agent or these

new combinations are supposed to be doing for you.

Then, you take that, and that, in a sense, basically tells you what is the outcome of interest that you are looking for, for this particular type of tumor, and what is the potential mechanism of action of the drug.

That will flow from that, what is the endpoint and what is the study design that you want to utilize for, at least from my thinking for the regulatory purposes.

DR. LINK: But I can think of a couple different scenarios. You can have a generalized protectant. You know, you have an effective therapy, you have a protectant, you want to add the protectant in the context of the current therapy that we know works.

But you could also have, I think what Roger is talking about, is a drug or an agent that is beneficial and may potentiate another drug or it may just allow to eliminate a drug.

So, if it was, let's say, a biologic that had very little toxicity, even if it wasn't better,

in other words, if you added it to the current therapy, if it wasn't better, if it gave you the possibility of eliminating a toxic agent, it would still be a worthwhile substitution. But there you are looking at efficacy, not protection.**

So, I can see even in a tumor that we don't have great therapy for, but the therapy is pretty morbid, that you would look for a drug that has some efficacy that would be a substitute rather than an add-on.

So, I mean we have to consider all the possible things that we might want to do, and that is more likely even.

DR. DAGHER: I think (a) was indirectly answered actually in some of the presentations and the discussion, it sounds like people agree that there would be value in some cases in having some kind of stratification even within, you know, a subgroup or within a histology.

But one potential pitfall is that you are getting into such small numbers, et cetera, et cetera. I guess I would then take (b) a little

further where we say, let's say that on balance, yes, there are pitfalls, but let's say we were going to use categories.

I guess my question is to kind of make it plain, I think Susan kind of put it in the context of you have got the medullos over here.

Numerically, you have maybe a few more numbers than in any of the others, and by the way, they are actually, to make it simplistic, you know, a different risk group than, say, the brain stem gliomas, and then maybe conveniently, or not so conveniently when we talk about the brain stem gliomas and the rhabdoids, et cetera, they are actually a higher risk than the medullos if you were going to make that comparison.

Maybe it's not an appropriate head to head, and since they are much smaller individual numbers, are you saying that maybe in some context, again, if the value is appropriate, or the agent that we were talking about would have enough of a rationale to apply across histology, one way of approaching it might be that you have refusal to

have a study in which those two or three histologies are included in the same study. That is how I would ask.

I don't want to put words in your mouth, but when, say, in (b), the categories in my mind, I am asking from a practical perspective when would you be comfortable enough with a category that you would--and I will use the word "lump"--together those two or three histologies, let's say, in the same study.

Is that too general a question?

DR. BLANEY: I think you would have to be very careful about doing that. One, you need to know the mechanism of action of the agent you are looking at.

So, if it's a general cytotoxic, you might consider that. But in looking at new agents, we are really trying to find things that are more targeted in the hopes that it will have a greater impact.

The other thing you have to look at is location of the tumor and the biology. So, the

brain stem is probably very different, you know, for whatever reason. We know from imaging characteristics, even though it is a high-grade glial tumor, that it is different than GBMs that occur in the frontal lobe or in the parietal lobe, so location plays a role as well.

I just lumped all those together as very much orphan diseases, so what are the histologies right now which is the best thing we have to stratify patients today, what are the ones we could theoretically do a randomized study in, which is a very small number, and what are the histologies that we are looking at, maybe 50 or 60 patients at most a year doing a nationwide or international study.

Those are going to have very, very different endpoints just because of the feasibility of what we are able to do.

DR. LINK: Stewart.

DR. GOLDMAN: The concept makes a lot of sense for reagents like a radio protectant or an otoprotectant, or something to help protect the

kidneys. But that seems to me would make sense and doable. I am not sure specifically treating a tumor.

DR. LINK: Malcolm.

DR. SMITH: I would see us probably going more in the opposite direction, that there is a real danger in lumping things. In fact, they may respond differently to radiation, they may respond differently to cytotoxic chemotherapy, so it is just one more variable that I think could create noise and risk us getting an answer that may not apply to populations of interest.

I think to go one step further, this talks about risk groups. But this morning we talked about biological groups, as well, and I think it is not just risk groups although I think the risk in the biology will intersect often. But we need to be thinking about the biological groups, as well.

So, we talked about medulloblastoma this morning, and so the sonic hedgehog pathway agent may be of interest for a subset of that, and so a biological subgroup. Within the standard-risk