medullo, we talked about the anaplastic group, taking that group out, so that you can make a more homogeneous group for a standard-risk medullo when you do treatment reduction studies.

If we understand the biology of anaplasia better, then, that will sector itself out as a biological group, as well. I mean I think we will be getting, rather than lumping for most studies, I think it will be important to stay with as defined a biology as we can, recognizing that the numbers are extremely challenging.

DR. LINK: I would presume we don't want to throw preclinical studies out the window. It depends on what agent you bring to us. If we bring a particular pathway inhibitor, you are hoping you have the biology that that would define the group.

That is why I think that the stratification, the high-risk stratum is basically who are we willing to not put on standard treatments, and go right to--I think we all agree on that.

Ken.

DR. COHEN: Karen, to answer your question a little bit more, I think the only place we have seen Phase III trials in pediatric brain tumors has been risk reduction trials.

I mean we get to a point with things like medullo largely, where we are essentially sort of saying we have gotten to a certain point, we have seen a good enough outcome, we have a reasonable number of patients, and now we are trying to do risk reduction.

So, for some types of studies that are based on the concept of risk reduction, whether that comes from substituting agents, whether that comes from radioprotectants, whether that comes from whatever, in those circumstances, I think risk reduction trial can lend themselves to some potential, and I think in some circumstances, as Dr. Goldman pointed out, I think to some degree of lumping depending on the nature of what risk it is you are trying to find some reduction in.

Otherwise, I don't think we have any provision for lumping histologies short of early

trials where we are just trying to get some handle on, you know, where we might begin to sort of direct our energies in terms of further use of the agent. But that is the only place I think where we have really done anything in the Phase III setting that has truly been dramatically--that we might ask an efficacy question in such a way that you could, in fact, consider a labeling indication, I think.

DR. KIERAN: I think the other thing is we talk about risk stratification. But when I first heard you say the word, I was automatically thinking of diffuse pontine glioma as the classic example, and then the first conversation was on the risk stratification for low-grade gliomas and standard-risk medullo.

In fact, I think many people would consider the least high risk or risk categorized things we do. I think the problem is that it is going to depend on who you talk to. I don't think anyone would deny that diffuse pontine gliomas are high risk, but I would argue that something like craniopharyngioma is also very high risk.

In spite of the fact that they all survive, they have a terrible quality of life, that the high risk definition we are using today was certainly different than it was yesterday and will be different again tomorrow in devising studies that use an arbitrarily high, medium, or low risk will therefore change over time, and because our studies go over long periods of time, one of the things we have all run into is the changing sands and the fact that people are now no longer willing to put their patients on this particular trial or that, because they think they know enough on their own not to do it.

The other thing that I think is going to be important in terms of the generation or the discussion of risk, if we were having this discussion a year ago, before much of the anaplastic or large cell medullo data was done, or on the other side, the desmoplastic in infants, which I would no longer really consider a high risk population anymore, at least based on two large studies now, that whole equation I think is

literally changing on a day-by-day basis, and therefore is going to have to be taken into account the way we develop these trials.

DR. PACKER: Can I go back to the diffuse intrinsic brain stem glioma? I think that we have done ourselves a little bit of a disservice as a specialty. We have gotten very focused on the diffuse intrinsic brain stem glioma, but I don't think that that prognosis is significantly different in a diffuse intrinsic thalamic tumor or non-resectable high-grade cortical glioma that you can't resect. I think they all do horribly.

We could lump those together. We could argue that we have enough biology if you buy it, that we have enough biology to say we want to use agents or agents plus standard treatment. Where a lot of it sometimes falls apart for those kind of studies is the question do we need a randomized trial, do we need a control group.

We haven't really addressed that again, but I think to be bluntly honest, if we put all those together and they are all sitting at about a

10 percent survival rate, why would a family enter a study that had a control group? Why would we need to have a control group if we have had 20 years of history?

I think where we left this in the May meeting is yeah, you can do it, and we will approve it for efficacy but we will never approve that for licensure because for that you need a real control group on, and then what is the advantage for the drug company to give us the drug if they are not going to get a license.

It is a very difficult approach for us. Even if we say we should lump and even if we say that we want to use biology, and even if we define out our high risk group, it is still not clear to me that we are going to get access to the drug in a timely fashion or be able to have that it's proven improved therapy.

DR. WEISS: I would just comment, I mean that is very good comments and actually, that is kind of a very good segue into actually Question 2, which is where we were really talking more about

what are the outcome measures, and we can't really talk about outcomes without thinking about what is the appropriate control that you would use to compare that outcome to, to really be able to have enough evidence of efficacy.

I saw a few more hands here for Question 1, but I would just say that I am certainly getting the sense from the group, and then I think we should get back and pick back up on Roger's question, you know, comments when we get to 2, as well.

It is very, very difficult to think about categorizations and that, in fact, except for the comments about if you have like a generalized protectant or possibly a generalized cytotoxic--but when we are evolving more into the field, it is a much more pathway-specific, that you really have to just think about the tumor and mechanism of action of the drug.

It probably isn't really feasible or appropriate to necessarily think about lumping for the purposes of at least drug development with the

exceptions that were already mentioned.

So, I mean I think that's helpful for me to hear about, and so I just want to say, I mean the discussion has been going well, I want to make sure that we get to the other questions.

I think in a sense we pretty much touched on a lot of 1(a) and 1(b) already that there are a number of different factors to consider, it's an evolving field, and you have to--it's very hard to give FDA a lot of general advice with the exception again of what was already mentioned about certain drugs that might have much more of a generalized effect, and then it might be appropriate to put a number of tumor types together into the generalized.

DR. LINK: Ian.

DR. POLLACK: I had a comment that maybe bridges into the next one. In terms of thinking about the risk groups, it sort of influences the type of trials that we can do for our good risk patients.

We have historically been able to do Phase

III randomized studies, we have done it for low-grade gliomas, we have done it for medulloblastomas, and although the current trials are in some ways therapy reduction, the previous medulloblastoma was a randomized comparison of two active regimens to see if one was better, and it was designed that way, and the same thing with the low-grade glioma study.

So, for those larger groups, it seems like it is reasonable to use standard Phase III type designs.

For the, quote "high-risk" groups, the ones where the one-year event-free survival is 20 percent, and we have a whole bunch of studies that show that, it would seem reasonable to have an entirely different design where we are looking at event-free survival or overall survival as the target.

DR. WEISS: Dr. Pollack, the comments you mentioned about the control trials in medulloblastoma, we were looking at efficacy, and that again is going to segue into Question 2.

The primary outcome of interest in those trials was overall survival or event-free survival?

DR. PAZDUR: Event-free.

DR. MEYERS: Just a brief comment about using the history of, you know, if you have a 20 percent, overall survival, whatever, progression-free survival. To use controls of that sort, I think it would be very helpful to make sure you are collecting all the data that you really want to know--that is, steroid dependence, or meeting developmental milestones even within that short period of time, because there could be no difference in progression-free survival but there is some other benefit for tumor-related symptoms.

DR. LINK: Before we leave that topic, I was under the impression based on the last meeting or the minutes of the last meeting that looking at brain stem gliomas, that you would have been happy to say you take a agent or strategy, to take an agent, and if you had--and it wouldn't have to be a home run, but it would be a double--that you actually improved things, that that would become

the new standard against which--that everybody would be happy that that would be a standard against which you would compare other agents, so that you are not demanding a necessarily randomized controlled trial. You may not license the first agent, but it would become--did I get that wrong?

DR. KUN: There was a lot of debate about that because, in fact, the recognition of that first agent was the first point that we were suggesting that hadn't been fully accepted by or, at this point, resolved as an appropriate trial endpoint.

Part of that was the discussion regarding whether or not we were looking for efficacy or not, but to take it to the next step implies that we first have broad recognition of that first step in brain stem gliomas.

That is what Roger was alluding to, and I think Ian as well, where the community is convinced that the data is quite solid, Jim can address this, and that the addition of any agent that statistically moves beyond that, we feel would

recognize efficacy.

Am I wrong, Jim?

DR. BOYETT: No, you are exactly right. I mean in diffuse pontine gliomas where we clearly know what happens if you use standard radiation only to treat them, and that has been repeated by multiple groups for decades.

So, the community simply would not do a randomized trial and have one of the arms standard of radiation only. The other thing I would point out is CG945 was for high-risk malignant gliomas, and it was a prospective randomized Phase III trial comparing two regimens so there are some high-risk patient groups that are still high risk, but do a little better than brain stem gliomas in which you can do Phase III trials in.

DR. LINK: Since we are talking about endpoints, maybe we should go to the second question because in point of fact, when we talked about that first trial that showed efficacy, it wouldn't be that it really cured a lot of people, it was more to do that you saw a favorable response

rate. So, the question is how do you define that.

So, the second question--

DR. KUN: You are referring to the same discussion now. We are looking at an endpoint of overall survival.

DR. LINK: I stand corrected then.

Well, let's look at response then or what would be considered an endpoint to measure that you would consider. Question 2. FDA considers a variety of outcomes as informative for assessing efficacy for regulatory purposes. Examples of efficacy endpoints include overall survival, progression-free survival, overall response rate and duration.

For each of the risk strata, or specified tumor types identified in your response to Question 1, if we really did that, please discuss study endpoints that represent a meaningful clinical benefit or a surrogate endpoint reasonably likely to predict clinical benefit.

In your discussion consider:

In what settings by population and design

is overall survival the appropriate endpoint for registration purpose?

In what settings can other endpoints, for example, progression-free survival, overall response rate be considered?

For progression-free survival or overall response rate, what methodologies should be used to define the endpoint and to minimize potential bias?

I think that third one may be the most contentious, but who would like to lead off this discussion since this was also one of the discussion points at the last meeting?

Malcolm.

DR. SMITH: In our traditional Phase III trials that people have described for medulloblastoma, the low-grade glioma, the high-grade glioma trials, we have always used EFS or PFS in the pediatric setting, and I guess, you know, it is just we have always done that in the pediatric setting, ALL, AML, our Phase III trials always have that as an endpoint.

I guess the assumption is that that is

likely to translate into a survival event, as well, if we had enough patients to do it with.

I think Mike was saying for the brain stem glioma where there is really no effective therapy now, and where, you know, we did discuss that there would be more confidence in a survival endpoint there, it wouldn't take that much longer to achieve the survival endpoint since the curve has basically shifted a year or so or less.

So, that was one place where I think there was a general sense that survival for brain stem glioma studies, at least with current treatments, that survival would be the most reliable endpoint there, and that comparison to the historical controls would give something that most of the pediatric community would accept as being fairly reliable.

DR. LINK: What about six-month progression-free survival for brain stem glioma?

DR. SMITH: When we are comparing to historical controls, and there was discussion there of looking at the imaging and swelling that may be

radiation related, and when does that resolve.

Particularly since you are comparing to historical controls that may have used different imaging methods and different criteria for progression, the sense of that discussion was that everyone would be more confident about a survival endpoint.

DR. KUN: I think the key thing there is you are not talking about tremendous differences in time that would demand marked differences in study design, and the curve that I showed that we had done on the analysis and the PBTC data, patients who were never called progression had the identical overall survival.

I just don't think we, at this point, have a means of accurately assessing that, that we would like to have.

DR. WARREN: One problem I see with this is numbers. So, we currently have a study right now comparing for patients with diffuse pontine glioma looking at two-year survival compared to historical controls, and in order to see if we

assume a 20 percent, two-year survival, we need 36 patients to show if it is significant if we see 40 percent survival at two years. So, we get into the numbers game.

If there is only 250 to 300 diffuse pontine gliomas in the United States each year, getting a 40 percent response rate or survival rate at two years is next to impossible, where, to us, it would be more interesting if you see a 30 percent response rate. But then you would need many more numbers.

DR. BOYETT: I would just like to echo what Malcolm said. I think when you are looking at the endpoint, you can't lump all brain tumors together, and I don't think there is any argument about being able to call a progression in a patient with medulloblastoma, ependymoma, or something like that.

On the other hand, calling progression in a brain stem glioma is very difficult and probably can't be done very well. So, I think in brain stem gliomas, as we discussed, survival would be the

appropriate endpoint. For medulloblastoma, I think progression-free survival can base the information that you would need.

DR. PACKER: I am going to be a bit contrary to that. We have been stuck on event-free survival and progression-free survival for many years.

If you take care of patients, what they want to know right after you finish a treatment did it work at this point or should I jump to something else. Where we haven't moved in the brain stem glioma is to get an early marker of saying that things may have worked for a while but stable disease is not enough because you are going to die anyway in about six months.

Where we need to do these kind of studies appropriately is in early surrogate marker before progression-free survival, and certainly before survival, so patients who know they are going to fail can add something else to try to improve survival rates.

Whether that is diffusion or something

else and how we structure it is going to be how we--we really should be doing the new generation of studies, because all our patients we put on these Phase I studies, the tumor stabilizes.

In our hearts we know that in six months or nine months, that tumor is going to progress if we are that lucky, and the family said can I jump to another study, can I do a different investigational drug, and the answer as an investigator is no, you are stable, you stay on the drug.

But the reality of life is if it didn't go away, the high likelihood is that it is going to come back. Now, if we have a surrogate marker to say we haven't killed it all, and our therapies have not been effective, then we might be able to start making progress and add one thing on top of another thing to improve survival.

So, that is where I disagree with saying being happy with overall survival, or, for that matter, progression-free survival, if we could evaluate it.

DR. BOYETT: I think the reality is you don't have that marker. Until you have that surrogate marker, then, maybe we would do something different. But until you show it to me, I can't design around it.

DR. KUN: And the truth of the matter is it is not that any of us are happy with that endpoint, it is just where we are at this point in time.

If you look at the data on these studies, there are, for good and for bad, an increasing number of patients who are coming off and are shifting to studies that are available for progressive or resistant tumors, because the parents say okay, I have gotten five months out of this, I am not going to get another month, let's go to the next thing.

DR. LINK: Why do you need a surrogate marker for a disease that is 100 percent fatal? I mean you need the diagnostic slide or the diagnostic test. So, that would be the one that you wouldn't need, I would think. I am talking

about brain stem glioma now.

DR. PACKER: I want a marker of early failure. I want a marker that I don't have complete control, then, I can add something right away after I think I have worn off the efficacy of my agent, and whether that is diffusion, PBTC spent a lot of money trying to prove whether diffusion is going to be effective.

If we think that is the marker, maybe we need to start setting some studies up with diffusion being an early marker of failure and allowing patients to go on to other studies.

I mean I just think we have got to--we haven't made any progress in brain stem gliomas in 25 years. Somewhere along the line we have got to change the way we are trying to do this.

DR. WARREN: We are not even able to define progression. So, we just had three neuroradiologists and myself measure diffuse pontine gliomas, and not looking at them over time, there is a 68 percent variability in tumor measurements, and that translates into anywhere

from zero to 177 percent difference in measurements for tumors.

So, how can you say anything has progressed or responded when we can't even measure it?

DR. PACKER: I would not use volume. You are talking about volume, and I think we have all agreed that we can't measure that way. We need something other than volume as our outcome measure.

DR. WEISS: Actually, we want to hear you instead of us, so you can talk.

DR. ARMSTRONG: I don't want to take us off the brain stem glioma, so I will make the point and then we can come back to it in a second.

But when we talk about the endpoints, we have also got to go back to the realization that we have different tumors with different types of outcome, so the event-free survival question may be the really appropriate one for the brain stem glioma where we have, on average, six-month survival and we are moving to these rapid new drugs where survival is the question.

We have got another issue, and that is the low-risk medulloblastoma patient where we have got 80, 85 percent long-term survival. But we are also--this is where the late effects question comes in--we now have survivors of our low-risk medulloblastoma protocol from the early 1980s, who are coming back when they are 25 and 30 years of age, and they are having second malignancies in the field of radiation, or they may be having early onset of neurologic disease of adulthood because of the early therapy.

There is very likely going to be a loop back to us as current patients begin finding out about long-term survivors who were treated in the same way, and they want to come back to us and say this is great that we had survival, but I don't want my kid to die when he's 31, or to have alzheimer's-like symptoms when he is 37, so I want new drugs and new therapies upfront.

So, it is going to cause us to rethink what our front-line therapy is in terms of those real long-term late effects, and that is very

likely going to come as an advocacy from the patient population, and that is a different kind of question than the question we have of event-free survival in a very high-risk, unlikely to survive population.

DR. SWISHER: I didn't want to leave with the IPG talk either, but I have the exact same thing. It is different when you are talking about at the IPG that may get a year to two years versus somebody like my daughter, and I really like 37 years, because I don't think 21 is something that I should necessarily expect.

In a very personal way, my daughter is a low-risk medullo that is 7 years out, and she has hearing impairment, we give her growth hormone every night. We give thyroid every night. We are looking at an MRA possibly for vascular events from radiation. She is at risk for secondary tumors, whether that is from radiation or CCNU.

So, an endpoint of survival means nothing to me. An endpoint would be can my child live on her own, is she going to have a stroke about when

she is 14. Am I going to have to put her away when she's 18 because I can't care for her anymore, she is too big for me to turn.

It is a very different, it's a heterogeneous group and it depends what you are talking about, and I just wanted to echo that in a very personal way.

DR. GOLDMAN: I was going to say something different, but, you know, I echo what you say, and we have been doing some research looking at quality of life tools from the patient's perspective, and the issues we have as investigators aren't even the same issues the patients necessarily have at different time points in their lives.

These are very elusive goals to try to study and understand. But going back to pontine gliomas, I guess still one of the frustrations I have reflects what Dr. Warren said, and although I agree with Dr. Packer, we don't even know when to take a kid off study, and that has really been a real problem.

I think we have all experienced where you

had a child on a therapy, they officially come off study for whatever reasons, there is a commercially available agent. The child and the family want to stay on that medication, and then later we see that they are doing well and have a response.

Sometimes I think we even take the kids off too early on some of those trials, and that's a difficult endpoint to know what to do with.

DR. COHEN: I think the thing with the pontine gliomas, and I said this at the prior meeting, is we will know it when we see it. This notion that we are going to suddenly lose information about the really great agent that somehow we goofed because we took them off study a little too early, or we picked the wrong surrogate endpoint or otherwise, we will know it when we see it.

I mean we have not made any meaningful gains in that diagnosis ever, and the fact is, is that for almost all of the tumors in pediatric cancer, the meaningful gains aren't 2 percent, they are not the statistically significant clinically

irrelevant gains.

They are jumps. They are big changes in outcome. It's no one survives it at a year or 18 months to 50 percent of the patients are surviving, and while I agree that in other populations, toxicity has much more relevance, we are not there yet. I mean we are not even close to there yet in certain populations.

It will be nice I suppose when we have that issue to contend with, but these are not subtle. I mean the big changes in all the tumors for which we have had great success in pediatrics come with big incremental jumps in outcome, in improvement in outcome, not 2 percent to 3 percent to 5 percent to 10 percent. I mean that just isn't how we have found agents that have been worth developing.

DR. LINK: So, in what settings are these the right endpoints? Clearly, it is not low-risk medulloblastoma, that is not where we are looking, and what are the methodologies that we can use.

We are sounding like that response rate

and progression-free survival is not something that people feel confident about in measuring in brain stem gliomas. If three people sitting at the same thing can't even measure the tumor, it strikes me it is going to be very difficult.

DR. BLANEY: I think that is because right now we don't have agents that truly give us responses in brain stem gliomas. I don't think we need a surrogate marker. We never get rid of the disease. It is still there. The problem is we haven't eradicated it to start with.

DR. WARREN: Does anybody at the table know of any pediatric brain tumor that decreased in size only, not disappearance, but decreased in size translates into improved outcome and survival? I don't know of any.

So, if it just decreases, but it doesn't go away, I don't see how we can use that as an endpoint.

DR. LINK: Well, if a decrease in size makes it surgically resectable, I mean there is plenty of evidence for that, not in brain tumors

maybe, but it is not my area of expertise. But there is plenty of evidence that resectability is clear in many tumors to be the most important factor, and drugs that clearly produce response rates that are meaningful allow surgical resection.

DR. WARREN: And if you have surgical resection, you come off study.

DR. LINK: You are talking about a Phase II trial, but we are talking about the possibility in a Phase III trial.

DR. POLLACK: But there are some studies that have second-look surgery built in, and one of the aims of the ependymoma study is to determine what percentage of patients with bulky residual disease are made amenable to resection after a short window of chemotherapy.

That is one of a limited number of tumor types where it seems like that is a major aim. The other one would be the non-germinomatous germ cell tumors. In that setting, response would seem to be a worthwhile endpoint. But for the other tumors, probably not.

DR. DAGHER: What I was trying to just to clarify before, because I know the temptation was to jump to the brain stem glioma discussion for many reasons.

Malcolm, when you mentioned the medullos as a group in general, I know that there are subtleties about even subtyping those in terms of risk, et cetera. But, in general, your discussion of EFS was based on a randomized setting--correct me if I am wrong--where, for example, you are testing one or more combinations of cytotoxic therapy and you are looking at, focusing on efficacy as a primary endpoint. There, the EFS would be an endpoint that includes death, progression, or recurrence. Is that fair?

Because the discussion then kind of jumped to the brain stem glioma, I guess my question, part of this is when we are talking about that paradigm, was there much discussion of that, or was there a feeling that that is not a controversial approach there?

I just want to get a feeling for that

before we continue the brain stem glioma discussion and then the response rate, et cetera.

DR. POLLACK: It seems like there is a good reason to look at the endpoint differently for those two groups, overall survival for one, and event-free or progression-free survival for the other.

If a brain stem glioma progresses, they are going to die. If a medulloblastoma progresses, they could potentially be salvaged with additional therapy. So, using overall survival in that setting would be a much muddier endpoint, whereas, with brain stem, that wouldn't be the case.

DR. BLANEY: One of the goals is really to come up with endpoints for a pediatric-specific indication, and so when we are talking about pediatric-specific indications and doing randomized studies, we really have to get earlier access to the drugs, because what happens is that by the time they enter a randomized study in a pediatric trial, they are commercially available and people have a natural bias that okay, this is commercially

available, the group is going to look at it, so they are going to use it off label if their patient doesn't get randomized to the right arm.

It takes us even longer to do studies because physicians and patients have bias about investigational arms. So, just one of the pleas is to as quickly as possible to get earlier access to these agents, so that we can bring them in and do the proper study without a biased patient population enrolling on the trial.

DR. COHEN: I was going to go back to Ramzi's point a little bit, and Jim sort of said it before, which is it is easy to use events when you can see the event, so the reason it works in medulloblastomas is because most of those patients start off with no measurable residual disease, standard risk in particular by definition to a certain extent.

So, we know when they have disease because they didn't have it on their scan before. It is true in ependymoma, as well, to a certain extent, we can see. So, when there is no measurable

disease, then, events are very easily defined.

In the settings where we have measurable disease, by definition, so the pontine glioma patients, frankly, the low-grade midline lesions, those are the groups where we have much more trouble using endpoints and for very different reasons.

So, in pontine gliomas, we say survival, because survival is easy because it happens quickly and stuff. In low-grade gliomas, it is troubling because that is not a reasonable endpoint because they live a good long time. But yet some are in the process.

So, I think that the challenge is very different based on kind of a starting point for those tumors. I can tell you in tumors, when they are all cut out, if they come back, that is an event, and if there are there in the first place, they are never going to go away. It is much, much harder I think to make that distinction sometimes.

DR. KUN: I think you could make the argument that certainly for the enhancing midline

hypothalamic tumors and certainly for the metastatic embryonal tumors, that probably event-free survival is a very meaningful outcome.

We have the data where we could really look at that to document that. But from the standpoint of durability of response, time to progression, then, you can measure the efficacy of an agent against that.

DR. LINK: Are we helping you here?

DR. WEISS: I think we are starting to get some of that. You have the two extremes where it is pretty clear with the medulloblastoma being on one extreme, I guess, and then the brain stem gliomas on the other in terms of outcomes.

Then, you have got the areas in between that are a little bit grayish, that there is some where a PFS is probably appropriate, there is some where survival is perhaps better. Maybe if we could--well, Larry is just walking away, okay, we will get you back in--I was thinking if we could hone in when you come back, if you come back.

DR. LINK: Well, Karen, would it help to

define this as curable versus non-curable tumors? EFS makes sense in a curable tumor. I don't know that it helps much in a thing like a brain stem glioma.

DR. WEISS: Right, that's right.

DR. LINK: The question is whether that would help.

DR. WEISS: Yes, I mean if people agree on that. I mean if we could start to think about, the two ends of the extremes are I think pretty clear, and then there is areas in between, and I don't know. If we could actually I think just maybe focus on that for just another minute and come to some agreement on sort of where those areas are.

But anyway, if we could just articulate that a little bit, I think that would be helpful for the agency.

MR. LUSTIG: I haven't spoken up much because I am a simple person. I am not a researcher, I am not a doc, and I don't work at the FDA, but I think trying to be big picture about this, what I find so frustrating about all this is

that this discussion, and maybe it's implicit, but I don't hear it, and it should be stated.

This discussion about all these questions fails to start from the point of what we are trying to achieve. We don't have new therapies, and we don't deliver anything fast enough.

So, all of this discussion about what kind of endpoints we should have should be with the goal of accelerating development of therapies that will save more kids and reduce the morbidities in the ones that we are saving.

It is very frustrating when we sort of take it down to this level of detail, and I think I want to hear from you all at the FDA about, well, great, we are giving you or the rest of the folks are giving you recommendations about what some of the endpoints should be. But will those endpoints, will that definition accelerate the process, will it ungunk the system. If it won't, in my mind, I don't see the value in it.

DR. WEISS: Well, I think it will, to use your words, "ungunk the system," in the sense that

we can actually give the academic community and the pharmaceutical company that has these drugs, you know, specific information on what they need to do, how they need to study these drugs.

The faster access issue is really one that I don't think the FDA has a lot of things that we can do about that, because there are a lot of different things that are really beyond our control.

But certainly we can specifically tell people, because that is some of the issues in development is that they don't know how they have to develop drugs, where they need to go, and if we can get a consolidated series of recommendations that we can go back to our companies and tell them what it is they would need, I think that would really be helpful in terms of speed of delivery.

DR. KUN: I think that is very true, Craig, in fact, if you look at our ability to extract drugs to use them in pediatrics, the better defined our endpoints might be, the understanding for those companies, that will facilitate getting

the drugs into the system, and I think that is the value of this dialogue.

MR. LUSTIG: And I don't question that. I think what I am saying, though, is I would like to hear explicitly that as we define these endpoints, that indeed will help to achieve that more important goal, if you will.

It is not simply just defining it for the sake of defining it, and maybe I am asking for something that can't be achieved, but it is just frustrating to hear, and I have sat on ODAC panels, and it has been a very long time. It has been a very long time, and all of you are dealing with patients, and it is very, very frustrating.

But I think that if this discussion doesn't lead to--as we said, we need some breakthroughs, we desperately need breakthroughs, and if this discussion can't help us to advance to that point--and I understand that the preclinical development, I mean we have a lot of work to do--but if what we are doing here then doesn't set the stage for once it's in the clinical trial, to

get it rapidly moving into the patient population, so we can really save more lives and reduce these terrible morbidities that we are seeing, then, I guess I just don't see the value of coming up with this level of detail.

DR. LINK: Craig, in order to have--you need a trial--in order to have a trial, you have to have an endpoint that is fixed that you can design a trial around, so I think that this would help in terms of people that are designing the trials, they know sort of this is what I am shooting at.

They have to have a target to shoot--excuse--but a target in terms of is it response, is it survival, what is it that they can design the trial around.

DR. PACKER: But I think you are absolutely right, I think, Craig, you are absolutely right that we have argued endpoints for 25 years, and we have argued it from CT to MRI, and we haven't changed a whole lot of things.

People live, they die, that seems to be the endpoint. We haven't used endpoints that may

be almost as important, like quality of life endpoints in any of these studies. We go on the assumption that we know what we are talking about with these endpoints.

The statement was made we know when a medulloblastoma recurs, because we can see it except half of the ones that we saw that were recurrent when we looked at them, now, in the last study, were probably secondary tumors or neurotoxicity read as progression.

So, I mean we aren't nearly as good, and I suppose we could spend another 20 years arguing the endpoints again. I do think we have to make some leaps of faith somewhere along the line to try to get drugs a little bit faster.

DR. KIERAN: One of the problems here is we are trying to find an endpoint, and I think the conversation over and over again has been there isn't an endpoint.

There is survival in some circumstances. There is progression-free survival, or event-free survival in others. But I think what Ken said,

that sometimes things take big leaps, but many times things take small leaps.

If you look at the adult indications for the two drugs currently approved, those are both small differences. But after 25 years of going for any hit at all, I think, you know, to not pay attention to even some small ones, because we may be able to make some small incremental changes.

I think similarly that it is not just going to be whether you live or die, or the disease comes back or not, we have to be more flexible that sometimes the outcomes or the analyses be based, as we said, on things like quality of life, those kinds of components.

I think the way we can be more rapidly responsive to what is going on is to keep all of those options open, and not try and generate a method that we try to use that really isn't going to fit a significant proportion of the other cases.

DR. KUN: I think part of what is important here maybe for this side of the aisle, if you will, is that maybe some of these questions,

rather than arguing endpoints, is to recognize that there are measures that we need to better develop, and those things are more difficult to study in the context of clinical trials. But whether it is imaging or biological endpoints, I think they are critical.

I will make a statement because no one responded to it, and clearly there are emotions involved in Dr. Swisher's comment. Maybe it is because I am a radiation oncologist, but I think a final endpoint of an adult who lived independently is, in fact, a fundamental endpoint for any of these trials.

It is not always easy to measure and requires very long follow-up, but I would take your statement as literal, which we have always given, and that is, what you want is an adult who can live their own lives.

DR. LINK: I think we have been sort of working around that we know what happens at the extremes. But you were trying to get us something in the middle where we have, I guess these are

low-grade gliomas that you are talking about, that have an intermediate prognosis where we need better therapies, where the survival issue is a long wait.

I think they want what kind of endpoints would you use there to evaluate new therapies.

DR. POLLACK: I think for that progression for your event-free survival would still apply, because the goal, particularly for young children, is to try to defer radiation as long as feasible. It still, for event-free survival, could take a long follow-up. But it looks like that is around three or four years, or two to four years, depending on the agent.

So, it would seem like that would be a reasonable target.

DR. SWISHER: I sort of see this in three groups although it has been broken down into two groups. It is the kids that are going to die, there is the diffuse intrinsic brain stems. There's the ones that are the test of endurance that are going to be 7, 8, 9, 10, 15 years on and off treatment with low-grade gliomas.

Then, there are the standard-risk medullos that theoretically get cured but have the quality of life issues which aren't necessarily spelled out, and each three groups have quality of life issues.

On thing that Dr. Meyers said was about steroids, and that is a huge thing. The IPG kid that is 45 pounds, and you give him steroids, and in six to eight months they are going to be 90 pounds, and the parents can't turn them, and they can't get out of bed, and they can't go to school, and they can't go to the bathroom, and they have accidents and they are embarrassed, and it is a really big thing to decrease steroids in quality of life and pediatrics.

That is something that you are the first person that I heard bring up here today, but that is an endpoint that is important even if it doesn't increase length of time, it increases quality of life.

DR. KIERAN: So, going back to the low-grade glioma, in fact, to some extent many of

us are already using other endpoints. We typically use stable disease as a measurement of the response, and I recognize that both in the printed material and in the discussion, that may not be copacetic. But many of us, for example, also use stabilization or improvement in vision.

We get a number of referrals, and I think many places do this. If a patient's vision in an optic glioma is stabilizing or improving, we consider that a response, in inverted quotes, "whether the tumor gets smaller or not," which, in fact, I think for many of us they do not.

So, here is a case where many of us I think are already beginning to see other opportunities to use them, obviously--and Roger Packer would know this well--that there has been an attempt to try and develop a more formal ophthalmologic evaluation that would allow more systematic classification of that change, so that we would have more confidence in it as opposed to--because most of us can't really understand the ophthalmologic report anyway--so at the bottom it

either says it is better or it is not, as I think what most of us go on,

But there are probably defined characteristics, and you can really extend that I think to many of the different quality of life or outcome variables that could work in many ways - hearing, steroid use we have heard, et cetera, et cetera.

DR. WEISS: One issue, if I am not mistaken, a PFS kind of outcome actually does take that into consideration, so, you know, it is a little bit different when you are looking at just like response rate, you know, CRPR, what do you do with stable disease.

But if you are looking at a PFS, then, I think that is sort of considered in that, if you are not progressing, you know, you could be shrinking, stabilizing, but you haven't progressed, so I think that is to some extent taken into consideration.

I think I very much appreciate your comment about maybe trying to develop, depending on

the tumor, if you have got some type of optic chiasm tumor where visualization is really what you are looking at, and really honing down on specific areas for that, you know, that would be something that I think would be very useful.

Those people that deal with these things might look into developing those kinds of focused assessments that can be then transported internationally and across studies.

DR. KIERAN: But then it is interesting because we do the reverse. If you have a patient with an absolutely stable optic glioma, that has had a decrease in vision, we consider that patient progressed.

DR. WEISS: I think that goes to, I guess, the definitions. Maybe it's in that third bullet, if you talking about PFS, or ORR, what are the criteria to define that, and that brings us to I think some of the discussions that occurred in the January meeting about the fact that oftentimes it's a hybrid of both radiological and clinical symptomatic types of measurements.

It probably is going to depend on the whole location issue, where is the tumor and what are the symptomatologies, so it is not only what you can see radiographically, which may or may not be actual viable tumor, because you don't have the diffusion or the PET or whatever, but also the symptoms that also then have maybe some bearing on whether or not they are steroids.

You know, there is a lot of confounding issues I think in trying to determine how you define whether it's progression or even response rate even though a response rate seems to be kind of off the table for purposes of this disease.

DR. ARMSTRONG: I think that is a very important point and when we talk about looking at any endpoint besides disease-free survival, then, one of the issues that we have in looking at children treated for brain tumors is we may see improvements in function that are directly impacted by the presence or the absence of the tumor, and that is really clear.

But in children where we have aggressively

treated with chemotherapy, radiation, or neurosurgery, we also have the emerging pattern of toxicities, neurodevelopmental toxicities that are not necessarily associated with the tumor but with the treatment that we provided.

So, you may wind up having stable tumor, but functional deterioration, and the functional deterioration is not related to the tumor, but to the treatment that was previously used, and that is another confound that we have got to grapple with.

DR. PACKER: I guess what you are hearing from this side of the table is the issue of how much flexibility do we have in these endpoints to access drugs and to move them quickly into the area that we need them.

Event-free survival, progression-free survival, overall survival are okay endpoints. They don't fit every one of the tumors, and trying to force all those tumors, even in the low-grade glioma, my bias is enhancing low-grade gliomas have to be evaluated as far as efficacy, different than non-enhancing tumors.

Even enhancing medulloblastoma, non-enhancing medulloblastoma is different, so there has to be some flexibility in the process, and when we do all these studies--and Jim Boyett knows this better--we always size the study for event-free survival or overall survival, and if something else falls out, we are pretty excited. But it is never powered to look at that analysis.

You want the powered analysis, you want the results, and I just don't know how in the system, as it is set up right now, that we are going to deliver that for the majority of the therapies to get therapy to patients quicker.

DR. DAGHER: If I may, to Roger, when we listed sort of viable and PFS and ORR, there is two points. One is that we did want the discussion to be linked with populations and designs, and you have all been very helpful with that. The other point is that we listed PFS and ORR simply as examples, so if there are other endpoints, given a specific population or design that is being contemplated, we are very happy to hear that

discussion. We didn't mean these as exclusive in any way obviously.

DR. GOLDMAN: I hope I can articulate this well. The points you brought up are extremely important about some of the long term and late effects. But if one of the issues here is how to bring these drugs and make them more available to us as a labeled indication, those are issues that can be then charted over a long period of time and become an issue that we follow carefully, can be a labeling issue and not so much a drug availability, and still it's about survival and progression and event-free survival that really will get new agents to the market.

Those very important late effects, I am not denying, but would be a different monitoring.

DR. WEISS: Can I just then ask, I think we have had some good discussion and it will be helpful to look at the transcripts when this is all over to really hopefully consolidate things, because I know there has been lots of different discussions.

Maybe we can get to the next question in just a minute. But in terms of where a lot of tumors that might be appropriate to look at a PFS measure, and this is probably not again a one-size-fits-all, can we just get a little more discussion on what are the different measurements that would go into PFS, realizing that it might be different if you have got something that is affecting the optic pathways versus something that is in a different location?

I guess what I am looking for is do you feel that it is both a combination of not only the radiographic, however you would think about it, and realizing there is newer radiographic technologies, but both the combination of a radiographic measurement and some type of clinical or symptomatic measurement. But it would be somewhat tumor-location specific.

I mean not going to every single type of disease, but is that a reasonable thing, or should it be focused on really something that tends to be a little bit more objective, and even there, there

are some issues without, such as the radiographic measurement.

DR. LINK: The protocols that we write have a measure of when a patient comes off study. But it sounds like a lot of people don't necessarily believe them, or believe that they can reproduce them.

Larry.

DR. KUN: I think just as actually even the adults in malignant gliomas, which is a setting almost as troublesome as the brain stem gliomas, if you have a lesion which is fairly uniformly enhancing, then, the ability to measure that becomes a little bit more certain.

Certainly, for the seminal low-grade tumor in kids, juvenile polycytic astrocytoma, the vast majority of those are uniformly enhancing, and so the ability to measure them across institutions in a study is fairly good.

I think the criteria for progression, which would combine an imaging endpoint with a specific sign of present, for instance, visual

fields for those that are hypothalamic or involve the visual pathways, is a pretty objective measure for response.

Now, what that response means is another question. But I think most of us would be comfortable with that, and I would welcome Roger's comments about that.

DR. PACKER: Again, I think that the endpoints are okay. You take the best radiographic and you build in some clinical safeguards, they are okay. They aren't going to speed up the process, they are just what they are. They are what they are, and until we get better ones, they are the ones we are stuck with.

I think we have been very lenient lately in using the endpoints. We allow some of our studies 50 percent progression to stay on study, which I have always found pretty ridiculous, but it's the way we are starting to build things because of this being gun shy about calling things too early.

They are fine. It is not going to change

today. We need something better. I still come back to maybe we should be off of all of this and maybe if we believed diffusion, we should use diffusion for a diffuse intrinsic brain stem tumors and move along with that, and live with that for a while.

I don't know where the answer is, but I think they are what we have. I would like to have better surrogate markers, I would like to have faster markers, and then what I would really like down the line is long-term markers. But there are different levels of battle.

The battle right now for many of the tumors is keeping the patient alive to a point that you can even think about long-term outcomes. For them, I agree with Larry, I think event-free survival and some clinical parameters is probably the best we could do.

DR. BLANEY: I think I have to agree with Roger that the endpoints are only okay. Sometimes it's a matter if we are looking at radiographic evidence of recurrence after a gross total resection, it takes us a month sometimes to decide

whether it's progression or a change from radiation therapy particularly when you are talking about disease that is leptomeningeal.

So, it is not 100 percent. What we do is the radiologists call it very early, our imaging techniques are much better. People are starting to use stronger magnets. So, we are still learning a lot about what we are seeing on imaging. It is not 100 percent black and white, and sometimes it takes a biopsy.

DR. SWISHER: I have a question on endpoints. If you have, we will take medullo since we are talking about that a lot, 80 percent survival, and you get another agent that is, say, 68, 70 percent survival but the full-scale IQ 10 years down the road hadn't changed, even though the event-free survival was less. But the toxicity and quality of life has improved, how does that affect endpoints?

DR. LINK: That's a medical decision, not a licensing issue. It depends on what your goal is for the patient, and then you can balance risk and

benefit. But, if one demonstrated 70 percent and one demonstrated an 80 percent, I think that you would license both of those agents as showing active and being clinically beneficial, wouldn't you?

DR. WEISS: Potentially, and the issue that we will probably use part of the next question, which we should probably start migrating towards, is the issue of the effects, and there is both acute and then there is chronic or long term.

Of course, the long-term effects are long term and you are not necessarily going to even know those outcomes until many years down the road when, you know, you have already made a decision.

I mean the product drug may be licensed or may not be licensed for that indication but may be widely used. That sort of a separate issue about continuing is done very well in pediatric oncology to follow patients and look at late effects, to try to answer important question about our therapies and the toxicities and how to manage them. But those aren't necessarily--the data will not be

available on hand at the time to make approval decisions, because those are things that are many years down the road that we all have to learn from.

DR. MEYERS: I just wanted to emphasize that imaging characteristics are really a surrogate endpoint of clinical benefit and how the person is doing is a direct measure.

DR. COHEN: I think that one of the things that we are getting a bit confused about is drug development versus labeling, and what level of rigor we would require at that point.

I absolutely think that it's true that in earlier drug development, we are a little bit more loosey-goosey about some of these things because we sort of recognize we are out there fishing trying to get some sense about where to kind of move, so we overcall progression in some cases and we probably postpone it, and we sort of sit on it for a while in other cases. But I don't think that we think as a community that we have missed the great drug because we somehow goofed in terms of some early drug development decision.

Maybe we have made some subtle differences in our thinking, but I think that if we see something that comes out of that early drug development, which is not about labeling but about where should we invest our energies as a population with the patients.

Then, I think we will have a greater level of rigor in terms of how we are really going to define, are we seeing something here that is meaningfully different than whatever that comparator is, assuming we can find the appropriate comparator.

So, I think we have to be a little careful about the notion that, yeah, we do a lot of stuff in the interests of early drug development, I think very much different than what we might do at the point where we were trying to be a bit more rigorous about proving that there truly is a difference in the application of the agent.

DR. WEISS: Thank you. I think that is very well said.

DR. LINK: Why don't we go on to the third

question here, some of which we have actually addressed a little bit, so I think this may be a little bit shorter.

Question 3. Neurological outcomes are important measures of response to as well as toxicity of treatment. Neurologic toxicity may manifest early and/or late in the course of treatment or follow-up, and ways to assess these outcomes, and their impact on the patient, will vary based on age of the patient, the functional status of the patient, validity and reproducibility of the assessment tools, et cetera. Please discuss:

Acute effects (neuron-cognitive memory loss);

Late effects (cognitive - school performance - endocrine - thyroid, growth);

Age and developmental status-appropriate tools to identify/minimize effects of chemotherapy, radiation and surgical therapies on the developing brain and predictive models/markers for toxicity.

So, here we have already heard some of the

things. Does anybody want to lead off?

DR. ARMSTRONG: These are good questions to consider, because there are differences in the acute issues that affect the child while there is tumor presence or they are getting treatment for the tumor or it has been completely resected, and those have an impact on their day-to-day functional ability, their performance in communities, some of the things that I mentioned today.

There are clearly direct acute effects of some of the medications that we use in the treatment of children with brain tumors that affect fine motor coordination and that has an impact on school performance.

Those are relatively easy things for us to develop measures for. There are good measures out there, and we don't have to worry about how those kinds of things change that would mean that we would have to change the measure.

The reason I say that, that is one of the complications that we have had and a lot of the work that is looked at, sort of functional

neurocognitive assessment in children with brain tumors.

Because we are looking at children whose brain is growing, and there are developmental changes and differences in the abilities that they have, and functional abilities that are associated with specific underlying brain development, we wind up having problems, because we can't use the same test multiple times because kids are changing. It is not the problem with the tests, it's that the kids are changing.

The acute issue is not an issue because we can use the same test. We can use the same tests for the 2-year-old, the 2 1/2-year-old, the 3-year-old in that short period of time while they are being treated.

Where we run into difficulty is being able to develop agreed-upon measures that will help us to track what is happening as a function of toxicity over a period of time that is sensitive to the neurologic component and comprehensive enough, because assessment of how a child is going to be

doing in school, you know, as I outlined this morning, there are multiple pathways that we get to how a kid is doing in school.

One of the things that I didn't mention that we know occurs in the treatment of kids with brain tumors is fatigue, and having reliable measures of fatigue may have an awful lot to do with how a child performs on a memory test, or a measure of sustained attention, or how well they are doing in reading.

That is one of our real challenges is recognizing this isn't a--unfortunately, we can't come to the point of saying let's look at it then for free survival, is the patient alive or dead at X endpoint.

The measurement is a more complicated one, and first, to really have it be meaningful, it has got to be a multiple assessment, and that has been a challenge for us in large clinical trials and even in some of the smaller things that we have done.

I will stop there and open it up more.

DR. PACKER: Just a couple of points. One is that as you listed late effects and acute effects, I think as we are following this population farther and farther, some of the things we thought were only acute effects are occurring as late effects.

If you look at the Childhood Cancer Survivor Study, even although the data is somewhat dirty, there seems to be 15 to 20 percent of long-term survivors who develop what would be considered an acute neurologic event, migraine, stroke, motor problems which might be early parkinsonism, a lot of those other things that we never thought of as a late effect.

We thought of these as acute effects, and I think we have to be cognizant of it.

The second is I am not really sure how any of these things, especially the late effects, are going to impact how we get access to drugs, because I am not sure that we are going to be willing to wait 10 or 12 years in an intervention to determine if we can or can't use the drug.

So, I am very interested in what Dr. Armstrong said about if we can prove the theory that you have insults at a certain time in development which will set you up for later problems five or six years from now.

If we can use that reproducibly, to me, that is a better way as far as drug development to get to the issue of late effects, which by usual definition is five years or later after someone has survived.

I still think unfortunately that is something to be proven. It is a great idea and I hope that it gives us some ways to do this. So, that is my caveat. I think there is a blurring between late and acute effects. It is great for writing articles. It is not that great for taking care of patients.

DR. ARMSTRONG: Let me come back on something, though, that I had said earlier, and I was concerned that maybe I didn't say it as clearly or in the way that it wasn't understood in the way that I intended it.

I think one of the things that we do have to be aware of is as information about late effects come out on prior therapy, that may affect the way that patients today look at the trials that we are moving forward and may actually create an advocacy for the development of alternative drugs to what was successful in the past.

We have seen this a little bit with some anecdotal reports coming in from some of our centers on our ALL trials, because as we have begun to raise the question about the POG strategy of the 1990s with escalating to high-dose methotrexate, as families have begun to learn that there is a risk of long-term neurocognitive toxicity with that, we have got a number of our centers who are saying patients aren't enrolling on our trials. They are questioning this particular treatment strategy even though we have seen some real progression.

There was a nice editorial here recently on that particular topic.

So, I think that one of the things we have really got to be concerned about is that as we do

late effects research, the information that we learn about the 20-year survivor may wind up influencing the advocacy of patients today, of trials that utilize the drugs that we used 20 years ago, or advocacy for alternative drugs that don't have that kind of toxicity, or at least that we need to look at for that long-term toxicity.

DR. WEISS: The problem, though, that has already been said, I think by Roger Packer, is that you might have late toxicities that you know about 10 or 20 years down the road that will influence how you might treat your patient today. But then if you make modifications, you won't know if those modifications will make any changes, good or bad, until another 10 or 20 years, which is why I think your comment about looking at, in this case, surrogates for late effects is another serious crying need for the field.

DR. KUN: And those are being developed. There are some imaging surrogates now that at one or two years are predictive of neurocognitive outcome at five to 10 years.

Clearly, there are other areas where similar surrogates are being developed, so that there is some promise there.

Without debating semantics, I guess I would just say that in oncology, we consider something subacute if it's occurring between a few months and up to one or two years, and anything after that is late, and whether it has an acute onset or not, it is still a late effect of therapy, it is not something different.

DR. WARREN: I also believe neurotoxicity is an important outcome. The problem I have, though, is how do you define it. So, if somebody has headaches 20 years later, how can you attribute that to their therapy that they got now, and not something else. You can't really.

The other issue is right now our only methods of detecting it are either on MRI scans, functionally with neuropsychological testing, or histologically, generally, on autopsy, and we know that MRI scans don't correlate very well with the neuropsychological testing.

So, it's an outcome that is important but we need to define it and figure out how to measure it.

DR. COHEN: This is sort of an obvious point, but it bears saying. You know, we are sort of having a medulloblastoma discussion now, maybe a low-grade glioma discussion somewhere hidden in this.

Our patients and families will accept substantial toxicity for very high-risk diseases, and I don't get into late effects discussions with my pontine glioma patients and my rhabdoid tumor patients. I hope I do someday, but I don't.

So, I think that again it is an area where the utility of these discussions is really driven by that subset of patients for whom long-term toxicities are a realistic consideration. I will say that even the kind of question that was asked before about if you are 10 percent smarter and 10 percent less likely to live, that is an ethical dilemma, not a labeling consideration.

DR. PACKER: Can I comment on that? This

is going to shock Ken, but I disagree to some degree. I do have that late effects discussion with the rhabdoid patients, because we could treat them with craniospinal radiation at age 1 year and have a real shot at potentially curing them.

I think this whole issue is a problem that goes across all of the tumor types, to what degree are you willing to radiate or give chemotherapy to a diffuse intrinsic pontine glioma. It may be that you could delay death by 6 months by necrosing the brain stem.

I don't know, it is always an issue across all the tumor types and I do think, as everyone said, we need better markers, and we have done very little work on developing early markers for late effects.

We know it when we see it, because they come into the clinic, and they have late effects, and I will bet you that we could figure out a way to know it earlier. Maybe sometimes we don't want to find that out, because we can't do anything about it.

So, why are we trying to define it earlier if someone is going to deteriorate, and not be independent at age 20, when we know in our hearts they probably won't be given the therapy that we have given and how they have responded to that therapy.

There is also the issue that there are tremendous host vulnerabilities that decide if someone is going to be very damaged, and as we take a look at these mechanism ways to predict early damage, define early damage, use drugs to prevent some of that damage, we have to have a much better understanding of the host vulnerabilities or we are just never going to sort it out.

It is not a whole lot different than treating the tumor and understanding the biology of the tumor. We don't understand the biology of the brain that allows some children to get standard dose radiation therapy and get into college, while others can't really get out of grammar school without tremendous help.

DR. SMITH: I wanted to make a point that

relates somewhat to the last question and to this question, as well.

One general comment is I think over the last 10 years, we really have made progress in getting new agents, and thanks to FDA, industry, Best Pharmaceuticals, lots of different things. But I think if you look at the roster of agents on the Phase I consortium, the PBTC, there really is progress.

Craig, I know sometimes it seems discouraging, but looking from where we were 10 years ago, there has been quite a bit of progress.

I think a challenge is how we move from that Phase I roster to Phase II, to pilot studies, to incorporating them in the kind of studies that we are talking about now, and how in some ways that is as much on us as it is on the drug companies and getting the drugs. But I think there has been some good progress. There is still work to be done and still agents that we want that we can't get today, but that there has been progress.

As we look at these new agents, though,

sometimes there is a tendency to say similar to what happened with the POG methotrexate. The paradigm was that we were going to use methotrexate, you know, anti-metabolites, and we weren't going to have late effects. That is true in some cases that you can use anti-metabolites and not have late effects. But there were ways of using anti-metabolites and high-dose methotrexate at certain doses and schedules that clearly cause neurotoxicity.

I think as we move new agents into the brain tumor setting and combine them with radiation, or combine them with chemotherapy, or just use them, period, we have to really be monitoring closely for unanticipated neurological toxicity, particularly as many of these agents are signaling inhibitors that affect signaling pathways that may be important for neural stem cells, for angiogenesis, and making connections with brain cells.

So, I think this neurological toxicity question will be especially important as we bring

new agents into populations where there is a good chance of long-term cure, and to be looking very closely at two or three years up the road as early signals for whether we have really truly made progress at the goal that was discussed of having an independent adult who is going to be our outcome.

DR. KIERAN: I would say it is not that we ought to start looking. It is pretty clear that radiation and chemotherapy already affect those stem cells, already affect those angiogenic pathways, and already affect those biologic pathways.

I think what we are coming to learn is that the biologic drugs are not quite as specific and/or that those pathways overlap important normal functions and that there is no such thing as a free drug, that every drug has a toxicity.

The thing that I am worried about is that it is interesting how many times parents have said, you know, particularly when the child is diagnosed with a medulloblastoma, PNETs, those kinds of

tumors, what is the therapy to cure my child, and it is sometimes very hard to have families, and admittedly sometimes physicians, focus on long-term issues when there is a greater focus in front of you, and that is a child with a potentially fatal disease in the short term if you don't do something.

It is interesting how many families come back and say, "I wish I had heard, or understood, or you had said some of this before. I don't know if I could have heard it, or if I would have understood it, but these are things that are now much more important to me."

Certainly, I think many of the clinical people in the room will recognize that many of our families, the toxicity you end up with is what is unacceptable, and so for kids that are severely paralyzed, but alive, it is being in a wheelchair that is critical.

For kids that are weak in the thing, it is the weakness, and because admittedly, we all want our kids to be perfectly normal, and whatever they

are not becomes the level at which we are no longer satisfied and how we do that.

The other thing is we talked about surrogate markers. I totally agree that surrogate markers are important. But, to some extent, often surrogate markers are you give a child radiation. There are probably surrogate markers we could develop that would tell us as you radiate whether or not you are doing damage. But, to some extent, that just tells you what is coming.

We also have to develop methodologies that are going to deal with it. Much of the premise today was a discussion of how we are going to try and get drugs in rapidly, efficiently, move them forward if they work and don't.

It is interesting that in a group of people with this much expertise, as a general rule, one of the things we seem to have agreed on is that we don't even have really a marker, other than survival, which we have agreed is not good in many circumstances.

Most of us don't even seem to like MRI

scans, which many people would think is the gold standard, and if we don't even have that as a, quote, "surrogate marker" of activity, it is not surprising we seem to be flailing a little bit in what would be the best marker on which to get a drug in quickly and decide whether we want to keep it or not.

DR. PACKER: I will just go on the basis I like MRI scans. They may not be great but they are a hell of a lot better than CT scans were and a lot of other things.

To go back to Question 3, which is I guess what we were supposed to be talking about, my thought is until we get these intermediary markers, that late effects are not going to be terribly useful to this group as finding new drugs and new drug outcomes.

Maybe if we could come up with something that will give us information in 18 months to two years after treatment, or six months after treatment, then, late effects can be factored in. But until then I just don't see how that is

workable to get new drugs to families, and that is a terrible thing to say to families, that if you are going to go through some of these new drugs, I have no idea how it is going to really affect you 10 years from now, and to be bluntly honest, at this point I can't care, because I won't get the drug if I tried to focus on that.

This becomes a real issue as we are starting to get into some very interesting drugs that can affect the blood-brain barrier and that can affect angiogenesis. We are starting to see some very interesting acute things that we may be paying tremendous prices for, or not "we," our families and children will be. But we are going to push ahead, because we are trying to get more kids to survive. Whether that is correct or not, I think that is the direction most of us practice in. Unless you can come up with a different approach for us, I think we are stuck with it.

DR. DAGHER: There has been a general sort of discussion that there were imagings, that the surrogates we are talking about for the outcomes in

terms of, say, neurotox, et cetera, are likely to be imaging surrogates.

I was just curious. It sounds like there is already some in development, and I was curious to hear more about what those are or what are we talking about exactly.

DR. BLANEY: Markers for response?

DR. DAGHER: No, for toxicity.

DR. BLANEY: People are looking at genetic polymorphisms that may predispose patients to toxicity. There is ongoing work in that area.

DR. PACKER: I think there are radiographic things people are looking at. I think the St. Jude's group has looked at a variety of different ones. Dr. Armstrong left the room, he can talk about some of the things.

I think a lot of things are circulating around diffusion tensor imaging, changes in composition of white matter as early markers of toxicity. I think a lot of people hold that to be a possibility to look at it as a quick surrogate marker.

Also, I think we should really see if there are some very specific neurocognitive evaluations at 12 months that will tell us that someone will continue to deteriorate, that could be a quicker outcome. I think that is a little bit farther down the line.

There may even be changes in the cerebrospinal fluid, proteomic measures that will tell us that the nervous system is starting to fall apart or showing damage.

So, I wouldn't give up on the late effect markers. My only comment is until we get clear data, does DTI tell us that someone is going to have more intellectual problems, or stroke, or do something else later, until proteomics comes, until we have a specific marker for developmental age that suggests that this was really impaired, we are not going to be able to use them.

DR. MEYERS: Also, one of the developing technologies is looking at hypometabolism on PET scanning. Of course, those kinds of studies are extraordinarily expensive and not available widely,

but that would be another potential, looking at something very early, before there is any functional changes.

DR. WARREN: Although neurotoxicity doesn't seem to be the primary objective, I think it is important to state that it should be incorporated in all our ongoing trials just so we have this data to look back on later on.

One of the things we just completed was using spectroscopic imaging and comparing the results of metabolite ratios throughout the brain in nontumor-associated areas with 10 to 12 different neuropsychological domains.

Another, we had a heterogenous population enrolled including kids and adults. We were able to make some correlations, so that may be another tool to use in the future.

DR. LINK: Why don't we move on to Question 4, the last one. Sorry.

DR. DAGHER: Before we move on, I want to just make a comment that although this seems in some ways theoretical, one potential practical

relationship to the regulatory issues that Karen brought up in the beginning, and we have to discuss this more.

That is part of what I am curious about is that, for example, when we ask for written requests that include general descriptions of trial designs, often we focus on safety and also asking for designs that would address at least activity.

It doesn't seem to be terribly out of the realm of possibility that in some cases, maybe some of the issues that were just brought up in terms of this question, in terms of looking at not just activity, but also this issue of the surrogates, I wonder whether there could be discussion of when--I mean we would I guess have to discuss it further internally also--of when that could be actually part of the kinds of things we ask for as part of those written requests.

It seems to me (a) these are the kinds of things that sometimes can be very costly and could require a fair amount of infrastructure that perhaps industry could help with when there are

specific products where based on actual imaging properties of the products and other properties, it might make sense to ask for that.

I just wanted to make that comment because I don't want people to think that this is completely sort of something that we are only looking at something terribly futuristic from the regulatory perspective.

DR. BLANEY: I don't think that we are close yet, I mean I think that we need to continue to look, but I don't think that to do today is feasible. You are right, those things are very resource intensive, they are also very burdensome for families to come back for multiple scans that are associated with multiple sedations and being NPO for a child on steroids isn't an easy thing to ask of a family.

But we need to continue to look for those things.

DR. SMITH: Your written requests are often in populations that are Phase I and Phase II populations, so long-term survival will be limited.

I wonder, though, you know, Roger's question whether we could ask for this kind of neuropsych or neurological testing, and I would be interested in what people think about, you know, if a company is proposing a Phase III trial for a brain tumor population, in a population where there are long-term survivors, you know, should neuropsych testing at two years just be an expectation, if there are a group of long-term survivors, just to at least have some preliminary evidence that there haven't been serious interactions with the known neurotoxic agents that might be used as part of treatment.

DR. PACKER: It is an interesting idea. The question then would be if you are treating a high-risk type of tumor, a patient with a high-risk tumor, are you going to recommend that they all get baseline cognitive testing at a time when they have active disease?

If you see late effects two years later in these patients and you don't have a baseline, and you haven't taken the impact of having progressive

disease when they initially were placed on treatment, how are you going to evaluate that there was toxicity.

I don't disagree with you. I just think it is methodologically very difficult unless you have a baseline.

DR. SMITH: I was referring more to the situation of a newly diagnosed population where you anticipate at the end of the day that there are going to be a substantial proportion of long-term survivors, and if an indication is being sought now in that population, whether the expectation should or should not be that there would be whatever neuropsych testing was appropriate to at least get preliminary evidence for the relative safety, neurological safety.

DR. BLANEY: I think it's a reasonable thing to do. But I think there is going to have to be a carrot in order for the companies to continue to do it, because otherwise they are just not going to bring the drug forward. There is nothing for them to gain.

DR. MEYERS: Can I say that the carrot may be that it broadens the scope of approvable endpoints. At least in the adult world, this has become increasingly acceptable and I am very busy, which is good, to get baseline assessments and then assessments at intervals that are appropriate to the disease under study as secondary endpoints, because of survival, of course, and all that. But if it turns out that there is no difference in survival, but there is reduced toxicity compared to the gold standard or to some other, that may be an approvable endpoint.

DR. BLANEY: But an approvable endpoint from the company perspective doesn't mean anything as far as the pediatric approval endpoint for the brain tumor population.

DR. LINK: Danny, last comment?

DR. ARMSTRONG: I think Roger's comment is a good one. But I think we are pretty close to having strategies where you could, in a broad brush stroke, be able to determine the level of function in a general sense at the time of initiation of

therapy that would not be too costly and not be terribly burdensome to the family with a couple of very specific kinds of tests that might take just a few minutes to be able to administer, so that you have got a picture of that baseline functioning with the idea that, as Malcolm suggested, then, your follow-up is the more thorough evaluation across multiple domains of function.

You could build on the model as we test it out, that I mentioned this morning, where you can then develop that kind of predictive relationship that in the next iteration would allow that to be a potential marker.

DR. LINK: Could I move on? Last question. Again, some of this we have talked about.

Question 4. New agents could be licensed on the basis that they demonstrate a reduction in toxicity without a decrement in efficacy, for example, a drug designed to obviate the need for or to minimize doses of radiation.

Such a claim usually necessitates

evaluation in the context of a randomized, controlled non-inferiority study, which we heard something about this morning.

However, such studies are particularly challenging when there is uncertainty regarding the active control effect size and when there are limited numbers of patients with the disease.

Given the constraints of non-inferiority studies, please discuss in what clinical settings a non-inferiority study should be conducted in pediatric patients with brain tumors.

I think we have sort of talked about this some, if anybody wants to sort of highlight some of the things we talked about earlier.

DR. REYNOLDS: It would seem from what was presented on non-inferiority studies that the number of patients required for those would preclude doing such studies. Could the statistician comment--but I mean I saw numbers of 800 patients. That would seem to be beyond what we could do with pediatric patients.

DR. SRIDHARA: It would depend on what

effect you have and what percentage. I took as a hypothetical example there was no drug there, it's just a number that I took and gave you, that that was the hazard ratio.

But if you are saying that there is a lot more improvement and instead of the hazard ratio being 2, it was 4 actually, then, the sample sizes would be different.

In all this, in considering non-inferiority trials, we have to know what is the control and what is its effect size, so that is the bottom line for non-inferiority. But I will say that when we are considering an endpoint, we want to make sure that you can measure it reliably and reproducibly.

So, it doesn't matter whether it's progression or response that you are measuring or any of the neurocognitive measures, or even--I thought it was interesting earlier it was brought up about the vision impairment part of it.

It is a very good endpoint if you can measure it and measure it reliably and reproducibly

you can use it, and I think that is where you have to decide what is the endpoint that you want to look at.

DR. LINK: I think we indicated in some of these tumors we actually have a large effect size for the standard treatment, so that it may actually make it--I haven't heard from a statistician that it is still feasible, but we would like to see if it might help. But that is certainly a starting place where we would do it.

DR. KIERAN: I think it is fair to say there are probably only a couple of tumor types in which we could really be talking about these kind of trial designs. Medulloblastoma, although we talked about the historical medulloblastoma, which includes a lot of histologies that are likely not going to be included in subsequent studies, so that population is only getting smaller.

We have talked about diffuse pontine glioma. But the dream of doing randomized studies, which means we have already got something active, I think that is probably a long way off.

We talked about one example again of a high-grade glioma randomized study, although admittedly I don't think Jim mentioned, but there was a large percentage of patients who actually didn't even have the right histology on that, that would not have been eligible, and certainly it wouldn't be replicated in subsequent studies.

So, the number of times we are actually going to kind of do these I think is limited, and I think as the biology progresses, a low-grade glioma, which we have often considered, and as you saw from the results recently, just ran a very large, well-run randomized study, we are beginning to segregate those patients in a number of different ways, both histologically by classification, Grade 1 and Grade 2, and by location, as well as within and without NF1 status, and the ability to keep lumping I think is going to become more problematic.

This kind of study design I think maybe had three or four options, and I am guessing that those are going down, and that for many of the

things we are trying to do for many of the diseases we see on a regular basis, for which we don't have good options, and for which there are not even going to be good adult counterparts, you know, we haven't talked about craniopharyngioma and choroid plexus carcinomas and PNETs, pineal blastomas, all of those kinds of things. We are going to have to come up with those, likely never in this kind of design format.

DR. LINK: Just remember when you eliminate--back on the standard-risk medulloblastoma, and you eliminate the bad guys, you actually increase the effect size and the control sort of things.

Does that help? Does that help your study numbers when you do that?

DR. SRIDHARA: Yes. I think you really have to ask the question when do you really want to do this non-inferiority study. You know, what are the suggestions that you would consider.

I think you would rather have a superiority study where you want to show that you

are progressing rather than just showing that you are non-inferior to already something existing.

DR. PACKER: To look at your question, my initial knee jerk was to say never and to move along. We haven't given you exact numbers, we haven't given you exact scenarios, but I would suggest that Dr. Pollack, from the COG, could probably give you survival numbers for four of our populations and what the questions we are asking, and I would be pleasantly surprised if you will ever come up with a hypothetical situation that we could do the non-inferiority studies as they were initially described by you in the beginning.

Now, there may be other non-inferiority studies. Since I have an inferiority complex, I am not really sure what I am talking about for the moment, but, given that, maybe we should give you some numbers and then you could tell us if there is a possibility for a non-inferiority study, and if there isn't, maybe we should think about other designs, and not get worried about this study we can never do.

DR. LINK: Pediatricians are mostly greedy about survival, you know, we need something where you have long-term survivors.

DR. WEISS: I know there are some hands over there, but I would quickly say, too, that when Raje presented non-inferiority, I mean we are talking about something that doesn't have any other advantage.

You are talking about two things, you want to show that something that is not much worse than something else, which I think everybody would agree isn't maybe a very interesting, important scientific question in this field.

So, it is really in a way, we kind of set the stage wrong for you, because I think what we are really talking about are things that do have some advantage, i.e., a significant reduction in the toxicity, for instance, so in some way there is a superiority in terms of toxicity, and you want to just make sure that you are not giving up too much on the efficacy.

It is not so much that you are giving it

up, you just have some uncertainty about what the true effect is, so it is how much uncertainty you are willing to live with for the sake of a known benefit in terms of the toxicity.

Of course, there, given the last discussion, we are really talking more about the acute toxicity, because, of course, the long-term toxicity, you are not really going to be able to even know until many years down the road, so it gets very complicated.

That is anyway just sort of what I wanted to pull out, because obviously, Ian has shown that you have shown, and the field is all agreed upon certain types of treatment strategies that do have these kinds of superiority in one aspect, and not really significantly worse on the other aspect, which in this case would be the PFS type measure.

MR. LUSTIG: This is a really important point and I think that, with all due respect, Malcolm, this is really where I get frustrated because candidly, families and patients are very concerned about this.

I understand that the parents come in and all they want to do is it is critically important to save the kid's life. But these questions about how do we identify some agents and get these things quickly evaluated and approved that will indeed provide, if you will, parallel survival benefit while hopefully ensuring some reduced toxicities, is extremely important.

I think that the question in my mind--we have to flip it on to Ted, and maybe that is what we are hearing--is what are the innovative designs that the FDA will find acceptable in order to get these things moving.

This is critically, critically important, because we heard from Dr. Swisher, and as we see the emergence of long-term survivors with these terrible morbidities, we really need to be addressing this kind of question I think now and trying to do it in as innovative a way as possible.

DR. SMITH: Before, I wasn't trying to say that neurological toxicity wasn't important. I think the point I would make is just I could give

you 10 or 12 agents now that we could combine with standard medullo therapy and try to reduce radiation, and the challenge in some ways is picking which of those agents you would combine with standard therapy and the pilot studies that you would need to get there.

I think the challenging part for this discussion is once you get there, how do you do the trial, so that you can say, well, survival is not compromised much, you know, that is important, and at the same time, that the quality of life is actually better.

We have been playing this game of pediatrics a long time of how do you get the best evidence that you can in a limited size population, and so we have done the kind of studies that Ian was describing, where we have tried to back off on radiation, you know, we are on our second generation of studies where we are trying to back off on radiation and use the chemotherapy agents that we have to improve outcome, outcome specifically, you know, the quality of life, the

neuropsychological status of the survivors.

I think our challenge is just, you know, that is where we are at, what risk are we willing to take that we are going to go from this maybe 80, 85, depending on how you take out the bad actors, maybe even higher, what risk are we willing to take that when we reduce radiation further, or when we add a radiation protectant, that outcome isn't now at 70 percent and that we have harmed a number of children who might have done quite well.

It is a matter of numbers. It is a matter of taking what risks that are appropriate to take in terms of decrements and outcome versus the potential benefits in terms of better quality of life, better neuropsychological status.

MR. LUSTIG: I think I would only--when we talk about "we," I think this kind of discussion, though, and, if you will, it is the philosophical discussion and the ethical discussion desperately needs to include the families in the community some way.

Maybe that is what is missing, because

those tradeoffs I think perhaps come differently for the docs and the researchers and the regulators than they may be for the community and the families.

I think that that voice and that perspective needs to be included as these kinds of things are developed. It is very important.

DR. SWISHER: I hear both sides of this and what harm is exactly in that 10 percent that you are talking about, that you harmed because they died, looking at a lot of the kids in the way that they live, I think that the parents and the kids might say that 10 percent, if it gives you a good quality of life, doesn't necessarily--it is not the harm that you think it is, that death sometimes is very welcome to some that have had a very, very devastating course. I would look at what harm is even if those percentages of survival go down.

DR. KIERAN: We do this every day. I mean we don't radiate babies with medulloblastoma in spite of the fact that we know we sacrifice enormously the cure rate exactly for these reasons.

The question is where are those boundaries, and there obviously isn't going to be a single number for a single study. It is going to be variable in multiple circumstances.

I thought when we had raised this point earlier, the question was both of those may be approvable circumstances and that which will itself raise some other issues in terms of better survivorship with a lower number versus higher percent of survivors but with the worst outcome.

I think clearly we are going to have to balance those but it didn't sound like they were mutually exclusive from the prior discussion.

DR. SMITH: I would just add, you know, I don't think it's an either/or. When you do the well-designed study, what you are looking for is both the survival and the quality of life, and you want to be sure that when you are doing a study, that it is actually that you have, in fact, improved the quality of life, that those children are doing better.

I mean I think that would be a commitment