good priority score and we send you a check. Then there is choice number two, which is a cooperative agreement which his more like a partnership between the grantee and the NIH where the NIH has some say about what projects are going on. Choice number three is contract, and most of our projects are done under contract. The point there is that the NIH is more in charge. So, you tell me it is going to cost you five million dollars to do something and I say okay, but we are running the show and this is what you are going to do. So, most of these have been done under a contracting mechanism as opposed to a grant or a cooperative agreement.

[Slide]

Just to let you know how this government contracting goes, it was news to me as of four years ago, is that we put together what is called a Request for Proposal, or RFP. That is how the government solicits for proposals. So the Request for Proposal, the RFP, is posted on a website called www.fedbizopps.gov, which is federal business opportunities. That is the website where

the government publishes its solicitations. The proposals come in and they are peer reviewed so in that way it is very much like a grant proposal. There is a special emphasis panel that is convened that decides whether the proposal fits the requirements that were requested in the statement of work and the Request for Proposal. Then the contract or contracts are awarded. In all cases, except for one, there has been one offer which has gotten the contract. The exception there, which I will get to, is the nitroprusside where we actually have two contracts, one to Duke and one to Stanford.

[Slide]

I wanted to tell you about studies that are ongoing under BPCA right now. We have several projects. The first one, which was the first off-patent Written Request from the FDA, is for lorazepam, Ativan, a very commonly used drug; no labeling for children. So, they actually split this into two indications. The first Written Request was for treatment of status epilepticus.

Study one was a pharmacokinetics study. That has been completed. Study number two is an efficacy/safety study comparing lorazepam to diazepam.

The interesting point about this is that it required exception from informed consent, which we did get from the FDA and so we are going through the community consultation procedure right now because it is impossible to get informed consent from a parent whose child is having a seizure.

The second project, again with lorazepam, is to look at sedation. So, lorazepam for sedating children on ventilators in the intensive care unit. This is actually a comparison trial between midazolam and lorazepam.

The third study is nitroprusside, and this was a study to look at the use of different concentrations of nitroprusside during surgery to reduce blood loss.

The lithium trial is in children with bipolar disorder. Again, there is no labeling for lithium in this population and we are looking at

the doses that are needed and long-term safety of this drug.

BaclofenB-this is using oral baclofen to treat spasticity in children with cerebral palsy. Now, baclofen only comes in a tablet. That immediate-release product is not available and we are actually sponsoring production of a formulation that is a liquid. So, this would be one example where actually this legislation has resulted in reformulation of a product.

[Slide]

Mark DelMonte earlier had mentioned the issue about preclinical studies. This ketamine product actually we didn't get a Written Request for but the drug was listed and there was certainly a need to look at preclinical studies in a non-human primate model to look at safety concerns, possibly as a preparatory point toward the FDA issuing a Written Request.

We are co-sponsoring a study of hydroxyurea with the National Heart, Lung and Blood Institute. We have a project going on looking at

preclinical studies of methylphenidate and a morphine study looking at developmental issues with morphine.

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The projects we have for oncology are four. Again, these drugs were listed. Vincristine is a study to look at neurotoxicity and pharmacokinetics in children and we are co-sponsoring that with the National Cancer Institute which has a cooperative agreement with the Children's Oncology Group.

Actinomycin-D are studies to evaluate hepatotoxicity, veno-occlusive disease and pharmacokinetics in children as well.

It also came up this morning about looking at long-term effects of these drugs, and the methotrexate trial in particular is looking at neurocognitive changes in children receiving two different regimens of methotrexate for high risk acute lymphoblastic leukemia, and daunomycin looking at the pharmacokinetics, safety and efficacy of daunomycin in relationship to body

weight.

[Slide]

I just wanted to pull out a couple of pieces of information about the actinomycin-D and the vincristine projects. Project one was looking at a chart review, looking at the demographics of the patients that had gotten these drugs; their treatment history, and the toxicity, the neurotoxicity and the hepatotoxicity. Peter Adamson's group is looking at a line-clearing method so we will be able to get PK samples back out of the central line instead of doing peripheral sticks, which is a huge problem; doing some pharmacokinetic modeling; and then sponsoring a prospective PK study for Children's Oncology Group.

[Slide]

So, in summary, this project has been a very nice partnership with the Food and Drug Administration and the NIH, and it is our responsibility to prioritize lists of studies for drugs and to sponsor clinical studies in children that will improve pediatric therapeutics. Thank

you.

Questions

DR. LINK: Any questions specifically about the distinctions between this process here and what we heard this morning?

DR. WEISS: Can I just ask a clarification question? I should know this, but I was just curious, you know, on the list I was struck by methylphenidate for ADHD which, of course, is used and I was just curiousB-totally irrelevant to this discussionB-what was the Written Request base for that.

Then the other question, you had a couple of them with disease categories where the area was clinical studies, like clinical studies in asthma, etc. So, the Written Request was not for a specific drug or what was that all about?

DR. ZAJICEK: Well, let me talk about the methylphenidate issue first. So, methylphenidate is on-patent. There is pediatric labeling for it. The issue about methylphenidate wasB-and this sort of came up emergently, that there was this article

in Cancer Letters a couple of years ago from El-Zein, and he was looking at children that, before and after they were put on ritalin, at cytogenetics. They found, I think it was 11 children. Again, they were using themselves as their own control and pre and post there were sister-chromatin changes. There were changes that looked like changes you would see in a child that had gotten cyclophosphamide or chemotherapy agents. So, there was a lot of concern that this drug, because it is used so commonly, was causing cytogenetic changes, serious changes so we felt that, because it was of extreme clinical importance, we should jump on this and do something. So, what we did was to fund studies trying to replicate these results and, luckily, they haven't been replicated. This is not the case. There was also a German publication, I think in the last week or so, that also showed they tried to duplicate these results and were unable to, which was a great thing. But that was the issue about the methylphenidate. I mean, it would be

very serious.

We are also sponsoring some preclinical studies in non-human primates as well, and also looking at cytogenetic changes there, looking at pharmacokinetics, and then also looking at developmental changes because, clearly, there seem to be some issues of weight gain and so on. So, we will be following these animals that have been treated out to their puberty to see if there are any differences. So, that was the issue about methylphenidate.

I am sorry, what was the second question?

DR. WEISS: The other one was just that you listed categories like asthma clinical studies. The Written Request seemed to be more of a generic broader area.

DR. ZAJICEK: Yes. So, the question here has to do with clinical trial design and exactly how to get at an answer. For example asthma, beta agonists, albuterol for example. There is a lack of labeling in very young children. So, exactly how you would go about studying those drugs. I

mean, you can't do an FEV1 in an 18-month old. So, exactly how would you study those drugs for those indications? Or, if you had children in an intensive care unit for example who were on extended amounts of albuterol, how do you fish out whether the drug is working, not working, is toxic and so on?

In other words, what has come out of this is not just the study of these drugs but exactly how to go about studying them. If we were given a Written Request, how would we bo about implementing a study on a certain drug in a certain population? So, I guess the issue that has come out is, you know, BPCA started out as let's do labeling studies, but there are a lot of other side issues hereB-formulation problems, clinical trial design issues, statistical issues and so on. You know, finding data in a database is amazingly difficult. You would think it would be obvious to know how many children got ampicillin last year. Good luck! So, there are a lot of things that have sort of come out, you know, frequency of condition,

frequency of use of drugs that have come out of this legislation that has been very nice, not just doing a labeling study. So.

DR. LINK: I just have one question. When actually a study is referred to the FNIH or the NIH who actually then sort of writes the WR? I mean, just fund the Written Request that was actually written by the FDA, or is it sort of then edited and revamped?

DR. ZAJICEK: This is how this works, so we get the Written Request and in some cases we have made some changes but the focus of that RFP, the Request for Proposal, is the statement of work so the RFP is this enormous, you know, 150 page document but there are two pages that talk about the statement of work. What is says is, for example, you know, for lorazepam for status epilepticus the Written Request has two studies, one for PK and for the randomized, controlled trial. So, the statement of work would have investigator able to recruit patients for a PK study and, you know, it takes apart the Written

Request in a very bulleted, blow by blow description of exactly what is required.

DR. LINK: But what I mean is you don't change the Written Request. That actually is what the work order is to implement the Written Request that comes from the FDA unedited, or do you actually take the liberty of sort of saying we have a better idea about how to study this?

DR. ZAJICEK: We have had a lot of back and forth with FDA about some of the Written Requests and there have been some changes made, not in all of them but in some cases. For example, it may be that the second study is highly dependent on study one and if study one fails you can't do a study two we can put out an RFP for the first study and then, you know, do another RFP for the second one.

As Lisa has mentioned, I mean, this is sort of an ongoing process for how these Written Requests come out. The first one, you know, was very different from the second one and third one so I think it has been a learning process for all of us to fish out exactly what we can do and can't do,

and so on.

MR. HUTCHISON: I am going to ask the official stupid question of the day so I will go ahead. My son is a neuroblastoma child and actually did six months of cis-retinoic acid, and it is a great drug for up-front therapy. So, I am just trying to understand before Dr. Matthay's and Dr. Reynolds' presentations, and you are maybe not the right person to ask this but let's say we go ahead. I mean, it is a great drug I am familiar with the I-Pledge Program but let's say they go ahead and ask for a Written Request. I wanted to ask this question before I hear the presentations. How is that going to benefit patients? I mean, they already prescribe it. It is already part of clinical trials. I think there is an open COG in combination with SAHA and it is used off-label all the time. So, I am just trying to think in what context would it add? Maybe it would help the prescribing oncologists with a little more flexibility. I am just trying to figure out why we are discussing cis-retinoic acid when the drug is

out there. I am just kind of curious.

DR. ZAJICEK: Well, I think the bigger picture here is the out of the United States problems. Just for example Japan. Japan does not have 13-cis retinoic acid. They don't have any Accutane in that country. Therefore, for children in Japan there is no 13-cis-retinoic acid, period. So, if a child gets neuroblastoma he is out of luck unless he goes to another country. That is my understanding for treatment.

DR. REYNOLDS: I would just clarify that acne is not a problem in Japan. They are fortunate. So, it is not a registered drug there. In speaking with the FDA equivalent in Japan and Roche, back when it was on-patent, it was clear that if there was a registry indication for it this could then perhaps drive the process of getting it into Japan. You know, we used to send it over there but we can't anymore because of the restrictions on the drug I-Pledge.

DR. WEISS: But if I can also clarify, Dr. LinkB-I think it is a very good question; it is not

a stupid question at all. But, remember, all of these oncology drugs that are on this priority list, 13-cis being just the most recent, are really old drugs that have been widely used, widely parts of, you know, major oncology regimens for pediatric oncology for decades. The criteria is can additional information provide health benefits. So, there is almost always information that one can learn from either a different population or different regimen, a different way to give the drug, better measures for safety assessments like the high-dose methotrexate that we discussed at another pediatric subcommittee meeting. The issue was whether or not there are new metrics for cognitive functioning using the high-dose regimen.

The on-patent process you heard about this morning is for relatively new entities that you really want to evaluate and that haven't been seen. The off-patent is really to take old things that may have been around a while and maybe everybody is comfortable with them, but to ask is there something more that we can learn from this. There

is no incentive because there is no more patent exclusivity available, but is there something where it makes sense to get some data and some studies. And, you can see that the off-patent from Anne's presentation this morning is much broader in a way than the on-patent. It really covers a much larger scope of issues in terms of the field and design, and even some preclinical issues. So, that is the question that is being asked of these older drugs, is there something that we can learn from them regardless of whether or not it is already approved, or not approved, or people can get it or not. Is there information that ultimately can help the FDA in terms of writing more informative labeling about the drug?

DR. ZAJICEK: Does that answer your question? Everybody is using it now so who cares?

MR. HUTCHISON: Yes, and it kind of bets the question if it is going to be for Japan. I mean we have two of the leading neuroblastoma people. We have Dr. Matthay and Dr. Reynolds here and I am, like, all right, maybe for JapanB-you

know, from the limited funding we keep hearing about as a patient advocate, NCI is losing funding and these guys, I mean they have other drugs in the pipeline so I am thinking, like, as a dad, I mean, we have two leading doctors here, should they be meddling around with cis-retinoic acid? Should the Japanese be doing it? And, should the Japanese be funding the NCI? Because, you know, there are limited funds here. So, I am, like, you know, is this the best use of their time? You know what I mean?

DR. ZAJICEK: Yes. Well, one thing we may be able to offer here, and I don't know if this is a possibility or not or still fishing around, but one of the main problems with the 13-cis-retinoic acid is the fact that it comes in this capsule. Right?

MR. HUTCHISON: It is a huge problem.

DR. ZAJICEK: A huge problem. So, if it would be possible to find a formulation that would be the liquid, that wouldn't be the capsule, you would be able to titrate the dose that would be

relatively stable, I think that would be huge. So.

DR. WEISS: Can I interrupt just to say that those are the specific questions that we are going to be asking when we get to those. So, I just wanted to make sure that you keep this in mind and provide that input when we get to those questions because we will be asking that.

DR. PAZDUR: But the major issue is to try to answer these questions. I don't want anyone to walk away that a major reason why this drug should be studied or other drugs should be studied under this program to provide information to the Japanese or some other foreign country. That is not the purpose of this program.

DR. LINK: So, the clarification is that the Written Request on this drug has not been written yet.

DR. ZAJICEK: That is exactly right. Yes, so nothing is a done deal here.

DR. LINK: First of all, before you get up, Pat, we have a couple of new introductions for the record. Go ahead.

DR. SANTANA: I am Victor Santana. I am a pediatric oncologist from St. Jude and a Washingtonian for this past year.

DR. LINK: Let's proceed now to Dr. Reynold's presentation on Phase 1 and pharmacokinetic studies and Phase 3 data.

Isotretinoin Phase 1 PK/Phase e Data

DR. REYNOLDS: I think before I start I will echo what Rich Pazdur said, and that is that there are a lot of reasons, as you will see in this presentation, why further studies, as well as getting formal data to the FDA on the use of 13-cis-retinoic acid will benefit children not just here but elsewhere. As Anne mentioned, that is one of many reasons but there are a lot of reasons and we will go over those.

[Slide]

What I am going to concentrate on is the preclinical studies and the pharmacology of the drug that led us to the point of doing a definitive Phase 3 study within the cooperative group, and then I am going to turn it over to Kate Matthay and

she is going to cover both the Phase 1 and the Phase 3 data on this drug from the clinical standpoint.

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To remind everybody what the effects of this drug are on neuroblastoma cells, it is a pretty dramatic effect, and this is MYCN amplified post chemo relapse neuroblastoma cell line. This is all-trans-retinoic acid, not 13-cis-retinoic acidB-we will get into the differences of those in a secondB-to get this remarkable growth arresting differentiation effect.

[Slide]

To remind everyone how these agents work, they are transcriptional regulators and there is a dog pile, if you will, of transcription factors that sit on the DNA component known as RAREs, or retinoic acid response elements, and the confirmational changes in this dog pile of these transcription factors that occurs when the binding of a retinoid to these is what regulates transcription and generally activating

transcription. In the case of this particular agent we are talking about, the activation of transcription leads to downstream de-regulation, if you will, of some targets such as the MYCN oncogene.

[Slide]

Note that all-trans-retinoic acid is shown binding here in 9-cis-retinoic acid, which are the primary ligands to bind to the retinoid receptors. 13-cis-retinoic acid really acts as a prodrug in this setting. It doesn't bind well with those receptors but it generates inside the cancer cell the ATRA.

[Slide]

This is just to review for you the retinoids, the common non-drug or vitamin that we know as retinol which can be converted into all-trans-retinoic acid, a process that is important to our vision. There is some natural isomerization of 13-cis-retinoic acid but it is a very, very minor component of what exist in nature and it is really, therefore, an ineffective

synthetic drug, if you will, and light can cause isomerization of that back to ATRA as well as certain events within the cell.

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Now, what got our attention about this particular drug was that certain neuroblastoma cells lines, which have been established from patients who had recurred after chemotherapy, could go into a long-term, as you will see almost permanent growth arrestB-maybe even permanent growth arrest; it is hard to measure these out that long-Bwith a pulse of ATRA initially when we were doing these studies and because at that time there was no all-trans-retinoic acid available for clinical studies, we focused on 13-cis-retinoic acid which turned out for pharmacological reasons, as I will show you in a minute, to be actually the right choice.

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These were the kinds of nonclinical data that led to the clinical trials that Kate Matthay will present to you in a few minutes where we

looked at pulses of two weeks of 13-cis-retinoic acid, and we were targeting getting in the clinical trial in our Phase 1 a five micromolar steady state level. So, we would get two weeks of a systemic exposure at about a five micromolar continuous steady state level. It is we hoped we would achieve. We targeted that in our preclinical model and ran these two-week on, two-week off pulses. As you see here, we didn't achieve complete growth arrest that sustained after just two of these for as long as we could measure it. The cell culture is pretty much, after 120 days, hard to measure. Concomitant with that is a complete down-regulation of the MYCN protein, the MYCN oncogene being one of the driving forces for a number of these neuroblastoma cells.

As we did these kind of nonclinical studies and did the Phase 1 study we found that the mean level that we got was seven micromolar in the Phase 1 study in a post transplant setting with a trough of four. So, we had reason to believe from these data that there would be the potential for

this to have some long-term sustained effects against neuroblastomas.

[Slide]

This is just reviewing for you from our Phase 1 study our pharmacology data where we saw the trough levels that you see here and the peak levels and, in particular at 160 mg/m^2, we were getting about a seven micromolar steady state level, as I mentioned to you. We were able to get above that without any really serious toxicities but there were a number of patients with hypercalcemia as you get into the higher levels. So, because we envisioned the long-term or chronic dosing of this, we then set the maximum tolerated dose at 160 mg/m^2 based upon really a chemical abnormality rather than a true toxicity.

Important to this is the fact that there are a number of children who probably are under-dosed at 160 mg/m^2 because there is great variability in the bioavailability of this agent, in the ability to deliver it, as you have heard, because of the capsules, and in the metabolism.

So, there are multiple opportunities here for us to refine the dosing and get potentially tumor effective doses in the children who might not get that simply because of the way we are giving it as we are giving it pretty much based upon this one single set of limited data in the Phase 1 study.

Why the two weeks on and two weeks off, it was really because of the initial experience with a trial that Jerry Finkelstein showed with the adult dose of it. The mucocutaneous effects were really setting in at about two weeks. So, we tried to dose escalate in pulses of this above the two weeks and give them two weeks off and that actually allowed us to get the MTD higher than what was seen in the adults where it was really probably the MTD for chronic dosing in pediatrics.

[Slide]

This is just showing that the systemic exposures are consistent with the steady state levels and they do increase with the dose, again making it important that we achieve the really correct dose, if you will, which may not be the

same for every child and is something that is worthy of study.

[Slide]

What makes this drug interesting relative to all-trans-retinoic acid is because to sustain differentiation in neuroblastoma, to achieve that long-term sustained growth arrest effect, we really need sustained chronic exposure to the drug for many days. As I showed you in the nonclinical data, we found that we need at least two weeks in two separate pulses across basically a two-month period.

With all-trans-retinoic acid, I will remind you that both in adults and children the systemic exposures decrease remarkably after just a couple of days of exposure because it induces its own metabolism. 13-cis-retinoic acid, as you see in these pharmacokinetic data, does not do that. We see occasional modest decreases in the systemic exposures that are ongoing across the 14 days of therapy but in general we see pretty steady state levels. So, again, it is acting as a prodrug,

delivering the ATRA without causing that induction of metabolism and the decrease in systemic exposure, which in pediatrics, as Malcolm can comment on because I know he was involved in that study, the doses are even less than you can give adults just because the ATRA induces super humerus cerebri, something that we see virtually not at all with 13-cis-retinoic acid.

[Slide]

We talked a lot today about formulations, and this is an opportunity I think for studying how to get formulations that might be better. Formulations are sub optimal for this drug. It is a liquid in a soft gelatin capsule and these are in 1, 20, 30 and 40 mg size. It can be pierced and when you pierce it you can actually chew it up. So, in some cases parents will pierce it and embed it in food and get the whole capsule in that way without leaking out the drug. But often in very young children what we see is that the drug is squeezed out into food or applesauce or something as a vehicle, and in doing that we don't know how

much variability we are inducing in the dose. It also is a problem because we are potentially exposing women of childbearing potential to a potentially teratogenic agent.

I don't know if anyone has ever read the instructions on a navy submarine, nuclear submarine for flushing a toilette but the instructions that the British provide to their parents to give this drug out of the capsule are roughly similar in length and nature. They are really complex, you know, double gloves; how you get rid of the gloves; how you dispose of all the components. It is treated very cautiously in the U.K. And, that may be why Gareth Veal has seen--who has been doing pharmacokinetic studies there, and this paper was published in the British Journal of Cancer earlier this year--that those children who are getting the drug out of the capsules were getting lower systemic exposures than the children that were getting the whole capsules.

We actually didn't see that much of a difference in our Phase 1 study but, again, these

are small numbers of patients that were studied and I think there is a lot of potential for out-of-the-capsule use of this agent for causing numerous problems, one of which is that, as we have heard from Neil, giving these capsules to children is not an especially enjoyable event for the parents. So, to try and address this, some well-meaning pharmacists have made extemporaneous liquid formulations and handed them out. The problem is they have not realized that in doing so they are promoting metabolism of the agent and so we have seen anecdotal-Bwe have no formal clinical data on this, but we have seen cases where children were getting pseudo humerus cerebri and we were very surprised at this because we don't see this with 13-cis-retinoic acid. When we inquired as to what was going on, it turned out they were taking these extemporaneous liquid formulations, and when the children were switched to taking the capsules the pseudo tumor cerebri was no longer a problem. So, I think this is another potential for unreported toxicities, again, because there is not

anything on the label to guide the parents, the pharmacists or the medical community in administering this drug to young children.

[Slide]

I want to point out that we have a lot of data that shows that in contrast to what you see with all-trans-retinoic acid in acute promyelocytic leukemia, you do not want to mix this drug directly with chemotherapy. We see for a variety of agents and a variety of cell lines that if we directly mix 13-cis-retinoic acid with cytotoxic therapy, as you will see here, the blue lines are the standard drug responses which are multi-log cytotoxic responses to etoposide, cisplatin, doxorubicin and melphalan, when you mix this with 13-cis-retinoic, the 13-cis-retinoic acid mightily antagonizes the chemotherapy. Time precludes me from going into several very interesting mechanisms about how this happens. It is not a sustained mechanism so once the children are done with the drug and if they relapse we don't see this effect, but direct combination would be I think contraindicated based

on these data. We have shown that in part this is really due to an induction of the B-cell-2 family of proteins by this particular drug while it is on board in the cells.

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So, with that in mind, we looked at how we would use this and what we thought the best way to do it was, as we see here with this schema of high-risk neuroblastoma, to try and come in and mop up. We can get several logs of induction with induction chemotherapy. The surgeons are able, in one fell swoop sometimes, to take out an entire log of tumor but that still leaves us even in the subclinical setting where the patients are in complete response with multiple logs of tumor that will cause a recurrence. The idea was that we could, hopefully, eradicate that by using myeloablative therapy to dose escalate beyond what the tolerance of these tumor cells is and achieve long-term event-free survival.

We also knew that quite infrequently a number of patients were relapsing after getting

myeloablative therapy so, clearly, even if they were in CR going into myeloablative therapy there were tumor cells that could recur. The idea was could we come in, in that setting and mature these tumors, these small number of residual tumor cells, using the 13-cis-retinoic acid and achieve a better outcome. That would clearly result in a Phase 3 randomized trial where you would have to look at this in that kind of context. There is no way to look for response. We are talking about treating disease you can't measure. Those results will be presented to you shortly by Dr. Matthay.

[Slide]

But before I turn it over to her, I just wanted to make a few suggestions, again in response to Neil's questions of how this drug and its use in pediatric neuroblastoma might be improved. I suggest that isotretinoin labeling should really include recommended dosing and approaches to administering this drug for pediatric oncology. There is absolutely no information whatsoever on this. For example, the Children's Oncology Group

has their own label. They have a monograph that the pharmacists hand out to people through the COG, but we really don't have a formal process and this is something that the label could really I think benefit people by getting that information out there.

Pharmacokinetics and possibly even pharmacogenomic studies might allow for PK or PG-guided dosing that would enable us to get systemic exposures that are optimal for children, minimizing toxicity and increasing the opportunity to eradicate tumor cells in some of these children.

Clearly, we need further studies on the administration route. If we are going to stay with capsules, in or out of the capsule is a question that has Gareth has really prompted by his studies in the U.K., and I think we really need to understand that in a larger number of patients and across the age range that we are dealing with neuroblastoma because there is a variable number of ages that we are dealing with and small children or very small children are very different than a

little bit larger children.

Finally, a stable formulation, as Anne suggested I think it is a great opportunity if that can occur, a stable formulation that is suitable for young children that could be safe for handling by women of childbearing potential would be optimal. I don't know if we will be able to achieve that but, if that could be achieved, that would be a remarkable advantage to these patients and something that would be really I think a true accomplishment to come out of this process.

[Slide]

Before I turn this over to Kate, I just want to mention that the clinical trials for the Phase 1 studies were done by Judy Villablanca and Kate Matthay chaired the Phase 3 study. In the cooperative group Bob Seeger has been involved from the get-go, as has the Children's Oncology Group. The pharmacokinetics were done by Vas Vramis and, most importantly, the patients and the parent who participated in these clinical trials, without which we would have no data. Thank you.

Questions

DR. LINK: If there are any questions specific to Dr. Reynolds' presentation you can ask them now, otherwise we will wait for Kate.

MR. HUTCHISON: This could be wrong. I thought I read back in Dr. Villablanca's Phase 1 going back to, like, '89 or '91, that for that specific trial she measuredB-I forget with it was PK, but the metabolism of cis-retinoic acid. Basically, I thought the conclusion was that some kids metabolize into the inactive forms, a prodrug for ATRA, but some kids would metabolize it into 4-cis-retinoic or 9-cis-retionoic acid. Is that right? I mean, do you guys already have some understanding? Did you already measure that in a clinical trial in the Phase 1? I know you don't do it for the Phase 2 because Sam was on the Phase 3 and didn't do any PK tests for Accutane.

DR. REYNOLDS: We did do PKs within the Phase 1 study. Those are reported in a small amount within the original paper that Judy Villablanca authored. Dr. Khan authored a second,

more intense paper focusing on the pharmacokinetics. And, we understand quite a bit about the pharmacokinetics from those studies, as well as from Gareth Veal's studies. But, again, these were done in small numbers of patients and one of the problems with doing the studies in those settings, particularly in Phase 1, is that you are often not using this in up-front therapy. So, I think we have less data than I would like to see in the younger children, which is really primarily where we use this drug right now up-front after myeloablative therapy.

MR. HUTCHISON: My follow-on question then, and this is purely conjecture on your part but I would kine of like to hear your response, since we are not measuring the PKs in kids in the Phase 3, getting Accutane, do you think they relapse because they are not hitting the effective level, or do you think they relapse just because they are resistant to this therapy? I was just curious what you think. For example, you know, my son was on it and relapsed while he was on Accutane. It is totally

conjecture but I am just kind of curious what your thought is. Did he maybe have a different metabolism? I am just kind of curious what your thought is on that.

DR. REYNOLDS: I think both from our data and Gareth Veal's data that there is the possibility that some children are under-dosed with this drug. There actually is a pharmacokinetic component, 973 was amended that was incorporated at the end of the study in the Children's Oncology Group. The only Phase 3 study, open, up-front study for neuroblastoma in COG right now is the 032 and that has the PK component for pharmacokinetics of 13-cis-retinoic acid incorporated into it and the upcoming COG Phase 3 study in neuroblastoma will have that in it. So, we are actually making the attempt to measure that. One of the things is, I think as we all know, that the cooperative group is short of resources and it would be very nice if the NIH, through the BPCA process, could help with that particular type of study.

DR. WINICK: Just a general question

because you are in drug development, liquids are very difficult. Are there non-oral preparations, patches, that would facilitate drug delivery that wouldn't be more dangerous? I realize that changes in absorption in changes in time of exposure changes all that. But is that an avenue that would be worth pursuing?

DR. REYNOLDS: For the amount of drug we have to deliver with this agent, I am not sure that patches would be appropriate. There is a powder formulation for another retinoid currently in a Phase 1 trial in neuroblastoma that might be suitable for this. I think there are other opportunities for delivering this outside of the capsules and I think we will just have to wait until people study what the optimal way would be.

DR. SANTANA: Pat, could you comment on two issues? First of all, how comfortable do we feel that we have defined the systemic exposure of this drug, that studies to look at both safety and activity based on systemic exposure and modulating that would be relevant?

Then, the second question is there is some emerging data in teenagers receiving Accutane for acne in which the absorption kinetics are different based on fasting versus food, and whether that would be relevant to a young population? It is kind of receiving chronic therapy because two weeks is kind of chronic therapy, and whether that would change anything in terms of how we would recommend that this drug be given? So, could you comment on those two things?

DR. REYNOLDS: Sure. I think that we need more data to understand what the systemic exposures are. I think, in my personal opinion, we have enough data with what Kate is going to present to you to understand what the likely toxicities are with this, but I think what we are more likely to be facing is a number of children who are under-exposed rather than those that might be over-exposed in this setting. But that is just a guess and I think we need a larger set of data to really comment on that.

With respect to food, food is a known way

of influencing the absorption of retinoids. There are recommendations for that within the clinical trials that administer this drug. We have not seen anything that we can tell obviously from the limited PK sets we have that there is a major influence of that because I think people may have been following on these Phase 1 studies close recommendations. But I think that there is a great opportunity there to increase the variability of this drug in terms of its bioavailability and, again, that is something that should be studied.

DR. SMITH: Pat, do we know if the ATRA levels change over the 14-day period? The cis-retinoic acid levels don't but do the systemic ATRA levels change?

DR. REYNOLDS: We have limited data on that, Malcolm, because we weren't funded to do that particular study so it is only a limited data set. But from that unpublished data it appears that the ATRA was consistent over the 14 days because we are able to measure ATRA in those patients. I think that is another question that really needs to be

answered. But it was my impression that we were actually able to deliver a higher systemic exposure of ATRA across 14 days with this than you would if you were giving ATRA directly at 60/m^2.

DR. LINK: As Kate is coming up, if we could have Dr. Maldonado just introduce himself. I have to say that you are here for the afternoon as well.

DR. MALDONADO: Sam Maldonado, industry representative.

DR. LINK: Thank you.

Cooperative Clinical Trials with 13-cis-Retionoic Acid in Neuroblastoma

DR. MATTHAY: Thank you and thanks, Pat, for setting the stage so well and discussing all the preclinical and PK data.

[Slide]

I am going now to review the cooperative clinical trials that we have done with 13-cis-retinoic acid for high-risk neuroblastoma.

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There have been really three trials done.

The first was actually done by Dr. Finkelstein in the COG as a Phase 2 study, and that employed the adult daily dose, as Pat mentioned, of 100/m^2 and we studied about 20 or 21 patients and saw only two responses so people were not very excited. And, that is why we went back and Pat had the preclinical work showing that we really needed to achieve higher plasma levels to expect to see an effect in neuroblastoma, and that the intermittent dosing schedule showed promise in these preclinical studies.

So, we then did a multi-institution Phase 1 study, led by Dr. Villablanca outside of COG, to look at it in this setting of minimal residual disease, which is where we really expected to see some effect from 13-cis-retinoic acid from the anecdotal reports we had in a few patients with relapsed disease in bone marrow only. So, that was a dose escalation study using the high-dose intermittent schedule in patients after transplant. Then, based on the tolerability in those results, we went on to do the very large Phase 3 randomized

study in the Children's Cancer Group.

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So, the Phase 1 study actually enrolled 51 patients, with a large number of courses because many patients, if they didn't relapse, were continued for 12 months on this treatment. So, there were 407 courses. The median age was 4 years, which is maybe slightly above the median age of a newly diagnosed high-risk neuroblastoma patient after 6 months of induction, but very close. The male/female ratio was equal. There were 6 patients with MYCN amplification and they were almost all autologous bone marrow transplant, which is generally now the standard for neuroblastoma. Most of them started their retinoic acid at 3 months post transplant. We had to wait until they recovered their counts and their ability to eat and their post transplant toxicity.

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The dose escalation started at the 100 mg/m^2 which was the established dose, and it was given in divided doses twice daily for 14 days and

then a 14-day break to recover from the somewhat unpleasant but tolerable side effects. The next level was 125 mg/m^2, then 160 mg/m^2, and then we went up to 200 mg/m^2.

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The dose-limiting toxicities on this study are shown here. We had 24 patients, 144 courses at the 160 mg/m^2 dose. We saw 3 patients with grade 3 skin toxicity; 1 patient with elevated transaminase; 1 patient with neutropenia, which is always a little hard to interpret in the post transplant setting as many patients have very sensitive bone marrows; and then 1 patient with grade 4 hypercalcemia. So, that was 5 episodes of DLT in 24 patients.

At the 200 mg/m^2 dose there was DLT seen in 6 of the 9 patients, given a total of 44 [sic] courses, and these were again grade 3 skin in 2; hypercalcemia in 3, of which 2 had grade 4 hypercalcemia; and 1 patient with anemia and thrombocytopenia.

So, on this basis, we stepped back to the

160 mg/m^2 tolerated dose. None of these toxicities were lethal or resulted in requirement for intensive care, and they were all reversible.

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Most commonly in these patients we see grade 1 and 2 toxicities, and cheilitis at the corners of the mouth is the most common toxicity, as well as some reddening, pealing and dryness of the skin. Diarrhea is seen fairly commonly though it is usually quite mild. Asymptomatic hypertriglyceridemia is also common. Mild elevation of the transaminase levels and then mild hypercalcemia are also seen as grade 1 and 2.

[Slide]

In trying to correlate the pharmacokinetic results that Pat discussed with the toxicity, patients who had a peak plasma level above 10 micromolar were seen in 6 of the 8 patients who had grade 3 or 4 toxicities. So, 75 percent of the grade 4 and 3 toxicities were seen in those with high plasma levels, whereas there were only 3 of the 20 grade 3 or 4 toxicities seen in patients

with plasma levels below 10 micromolar. So, the risk of toxicity was much higher if you had a plasma level above 10. Therefore, our goal should be between 5-10 micromolar.

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We did actually have a few patients with assessable disease on this despite the fact that they were post transplant. There were 10 patients with assessable disease and 4 of these actually achieved complete remission. I think it is notable that 3 of these responses were in bone marrow and we don't think that this agent is very effective, or we have not seen it to be very effectiveness in bulky soft tissue disease. Five of the 10 developed progressive disease while on retinoic acid and 1 patient has stable disease.

[Slide]

So, in summary in the pharmacokinetics you saw that there was a linear increase with increasing daily dosage, both in the peak level, trough level and the area under the curve. Also, Pat showed that the mean peak plasma level at the

maximum tolerated dose was greater than 5 micromolar for most patients and, again, that peak plasma levels above 10 are associated with the grade 3 and 4 toxicity.

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So, our conclusions from this study were that the maximum tolerated dose of the intermittent schedule of retinoic acid is 160 mg/m^2 divided to 80 BID. The dose limiting toxicities were hypercalcemia, some GI toxicity, some pancytopenia and skin toxicity. The plasma concentrations of 5 micromolar, which are those that produce sustained growth arrest in vitro can be achieved with acceptable clinical toxicity for most patients.

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Then, based on these results, we felt it was worthwhile to proceed with a Phase 3 randomized trial of 13-cis-retinoic acid. This was actually a study with two sequential randomizations. As I will show you, the first was bone marrow transplant versus continued chemotherapy. For the second patients were randomized to the retinoic acid to

test the effect on minimal residual disease.

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So, the aims of the study were, first to compare, by prospective randomization, the efficacy and toxicity of consolidation chemotherapy in standard doses compared to very intensive chemoradiotherapy with autologous bone marrow transplant. Then to determine, secondly, by prospective randomization, the effects of 13-cis-retinoic acid on minimal residual disease and on relapse-free survival.

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So, the outline of the study is shown here. Patients who were diagnosed with high-risk neuroblastoma, mostly stage IV or high risk stage III, underwent 2 cycles of induction chemotherapy and then were randomized to either go onto consolidation chemotherapy without stem cell rescue or to myeloablative therapy with autologous bone marrow transplant. During their induction, as well as a bone marrow harvest and purging, they also had surgery to their primary and local radiation.

Then, when they had recovered from their consolidation chemotherapy or transplant, at approximately 34 weeks from diagnosis they underwent, if they agreed, a second randomization, regardless of which consolidation they had, to get 13-cis-retinoic acid or no further therapy. So, we would essentially be left with four groups after this randomization, those who had gone through chemotherapy and then gotten retinoic acid or no further therapy and those who had gone through bone marrow transplant. And also eligible for the second randomization were patients who had refused the first randomization and just been treated with the consolidation chemotherapy.

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In total, this study enrolled 539 high-risk patients, of whom 379 accepted the first randomization and about 260 accepted the second randomization. The study was run from 1991 to '96 and the average age at diagnosis was what we see for high-risk neuroblastoma, 2.5 years of age. Eight-five percent of the patients entered had

stage IV disease and overall there were 40 percent with gene amplification of MYCN.

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I am going to jump now to the toxicities, and I am sorry for the typo, this is in 273 patients with retinoic acid. Those with hematologic toxicity grade 3, there were 9 percent. These numbers are all percentages, 4 percent had grade 4 and most of the hematologic toxicity was seen in the first 3 months of cis-retinoic acid closest to the time of transplant and, again, we think it was more related to the transplant than the retinoic acid itself.

There were 5 percent with hepatic grade 3 toxicities and only 0.5 percent with grade 4; 5 percent renal grade 3, 3 percent grade 4; GI toxicities, there were 3 percent grade 3 and no grade 4. Skin was about 2 percent each for grade 3 and 4; hypercalcemia, 1 percent grade 3 and no grade 4; and infection, 3 percent grade 3 and, again, most likely this was related to their post transplant state. So, overall there were 15

percent grade 3 or 4 toxicities in the first 3 months and only 9 percent in the second 3 months as they got further away from transplant. So, I think in terms of toxicity for such a high-risk disease this is extremely tolerable.

[Slide]

Now we will look at the event-free survival and survival on this study, and I am just going to show you the outcome of the first randomization. These curves now have 8 years of follow-up as the study has now been closed for about 10 years. You can see the numbers of patients surviving listed along the curve. For BMT, you can see that the curve levels for about 7 years are about 30 percent and for consolidation chemotherapy it is much lower, about 19 percent, and there was a significant difference by log rank analysis in event-free survival, favoring myeloablative therapy and bone marrow transplant.

Survival is an interesting analysis because you can see that the curves are almost superimposable and then actually cross at about 2.5

years. So, we did a log rank comparison of survival initially and showed no significant difference, but when we use a test of proportions, which is a more appropriate test to use when the curves cross and violate the principles that the average different between the curves should be consistent, you can see that there is actually a highly significant difference in survival for the patients undergoing bone marrow transplant on this study. Those analyses were performed close to diagnosis from the time of randomization at 8 weeks.

[Slide]

Now we will look at the outcome of the 13-cis-retinoic acid and these analyses, I just need to warn you because the outcome looks betterB-these are performed from the time of the second randomization so this is only looking at patients who survived consolidation and/or bone marrow transplant and then were randomized to either receive or not receive 13-cis-retinoic acid. The top curve shows 113 patients randomized to

receive retinoic acid and you can see again that their outcome by log rank analysis looks much better than the no 13-cis-retinoic acid but the difference is not significant. Again, the curves are very parallel to about 1.5 years out. So, it seems to show an advantage but this curve includes all the patients, those who got transplant and those who got consolidation chemotherapy.

[Slide]

If we look at overall survival, again we see a very prolonged overlap of the curves in violation of the usual log rank analysis. So, we did a test of proportions and again you can see that at 5 years the overall survival is significantly better for the patients randomized to receive 13-cis-retinoic acid regardless, again, of whether they first had a transplant or had consolidation chemotherapy. So, I think that this long-term follow-up of this study, which was initially published in 1999, clearly again shows this is an active agent and one that we should capitalize on possibly by optimizing its use which

might further improve the outcome.

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We also decided to look at patients who underwent both randomizations. So, now patients who refused the first randomization are excluded and we are looking at about 50 patients in each group who first were randomized to either consolidation therapy or transplant and then also survived and agreed to go on the second randomization. So, you can see that for patients who made it through both randomizations and agreed to randomization, again the curves layer out and we see a much better outcome for transplant with cis-retinoic acid compared to the outcome for transplant without cis-retinoic acid, and that is better than consolidation chemotherapy with cis-retinoic acid which is, again, better than chemotherapy with no cis-retinoic acid. In terms of comparing by log rank, the top curve, BMT with cis-retinoic acid to the bottom curve, there is a highly significant difference.

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Similarly, this is overall survival and here it is interesting that the consolidation chemotherapy curves really overlap for overall survival regardless of cis-retinoic acid, but BMT with cis-retinoic acid is still better than no cis-retinoic acid and significantly better than either of the consolidation chemotherapy regimens.

[Slide]

In conclusion, kind of ending with what you probably knew you were going to hear, I think we have shown that both myeloablative therapy and post myeloablative therapy with high-dose pulse cis-retinoic acid improved event-free survival for high-risk neuroblastoma. We also saw a very significant increase in overall survival for ABMT and cis-retinoic acid and it is highest for the patients randomized to receive both.

Just as a footnote, I wanted to mention that the European cooperative group ENSG, also did a randomized study with 13-cis-retinoic acid and showed no improvement in outcome. I think the main reason for this is they designed their study before

our Phase 1 results had been published and they used a dose that was about 15 percent of the dose that we used here and they showed absolutely no difference. So, I think the dosing, pharmacokinetics and getting a better formulation are very important. Thank you.

Question

DR. MORTIMER: Is there any correlation between toxicity and efficacy? I mean, certainly with the tyrosine kinase inhibitors we all focused on cutaneous side effects being a marker of response. Is that true with 13-cis? Is there a correlation between toxicity and outcome?

DR. MATTHAY: I don't think we have tried to look at that. It is something I guess we could look at with the patients who had grade 3 or 4 but the problem is there were so few patients who had significant toxicity that it would be difficult to look, and every patient who takes their medicine gets cheilitis and skin abnormalities during the time they are on it. So, it would be a difficult question to show statistically.

DR. LINK: I just want to clarify one thing. If you analyze the study as designed, there was actually no significant advantage for retinoic acid.

DR. MATTHAY: No, the study actually initially was designed only to use the test of proportions actually at three years. At the first analysis there was not a significant difference. At the second analysis, the updated analysis, there is a significant difference.

DR. LINK: In event-free survival as well?

DR. MATTHAY: Yes. That was the point, and we actually could comment a little more on this. It is really interesting that the curves separate so late after the second randomization, and that suggests to me that again the patients who have maximal minimal residual disease, as it were, who have more disease even though still minimal or microscopic are probably those who relapse in the first year or two and cis-retinoic acid may not impact those patients but perhaps it impacts the patients who really have very small amounts or

perhaps, for some reason, whose tumors are more amenable to differentiating effects. I don't know the answer to that. But it is very interesting that it is so long after the treatment when you see the difference.

DR. LINK: Any evidence that you should continue beyond, you know, like chronic maintenance for years and years?

DR. MATTHAY: That is a question I think that every parent asks and we don't know the answer to that. In our Phase 1 study we treated for a year. On the Phase 3 study we actually only treated for six courses, for six months. I think we don't know that there is any benefit. We do know that there are patients who become resistant to cis-retinoic acid and relapse. So, our conclusion, unsupported by data, was that if you hadn't seen an effect by six months or if it didn't work in six months they probably had some resistant cells which would eventually emerge. But I don't think we know the answer as to whether it would chronically suppress the disease longer. I don't

know of any harm. We have certainly had many patients we have treated for two or even three years with retinoic acid without any noticeable long-term side effects, but those patients haven't been followed for 15 or 20 years.

MR. HUTCHISON: Thanks, Dr. Matthay. Going back to my question for Dr. Reynolds and you also, with the number of children that have been on 3891 and 0032, and we know the in vitro data says if you achieve greater than five micromolar, you know, that is plasma level you want, but it sounds like we have done PKs on ANBL0032. I was wondering can you associate those PK with responses? You know, do you have the data to go back and look at the children and say these children achieved a PK above 5; these childrenB-

DR. MATTHAY: So, we can't look at responses on our current study, and the reason is children are only permitted to go into the randomized portion of the study who are in complete remission. If they had any detectable disease they would be non-randomly assigned to the antibody arm

or go onto other therapy. I think that, hopefully, if we can get enough PK data, and that is going to be difficult because it is a voluntary part of the study, but if we can get enough PK data we can then go back and look at relapse-free survival. That would be our goal, to associate relapse-free survival with the pharmacokinetics data.

MR. HUTCHISON: But we don't have enough data for that right now? I mean, it seems like there has been a ton of kids on Accutane and that would be the question. I mean, do kids that don't relapse while they are on AccutaneB-are they the kids that are achieving their plasma level or not? But what I am hearing you guys say is you don't have enough data.

DR. MATTHAY: I don't think we have enough data right now. The study was amended to start collecting that data not too long ago. Pat may know how many patients we have.

DR. REYNOLDS: Just to comment, we have 26 samples in the freezer. Okay?

DR. MATTHAY: It is not enough.

DR. REYNOLDS: Yes, it will require the completion of the next high-risk study to get enough to answer one of the questions in this amendment to all of those studies, which is does the level correlate with outcome. Gareth Veal has tried to do this in the U.K. I think he is up to 33 samples after three years. So, this is a long process and I think if we pool our results together with them, you know, with some driving behind it from the NIH, I think maybe we can get the data but it will take a while.

DR. WEISS: Are you saying it is voluntary and so there has just been a reluctance for the families to basically consent to some of those additional procedures?

DR. MATTHAY: It is probably not just the families. It is probably the physicians because it is not very well compensated and it takes a lot of extra effort to both collect those in a timed way, to freeze them, process them, mail them. In general, we have not really wanted to or been able to mandate any pharmacokinetic studies even on some

Phase 1 studies for children because of the discomfort. In this study kids mostly had their central line removed and they have to be stuck. In other studies where drugs are given IV you have to have a separate IV to draw the PK studies. So, many times, particularly in this setting where kids are in remission, the parents are not willing. On the Phase 1 studies most of the time they agree because they want to move things along as fast as possible.

MR. HUTCHISON: [Off microphone; inaudible].

DR. MATTHAY: It is just a blood draw, you are correct, but it is an extra blood draw.

DR. REYNOLDS: This is Pat Reynolds. I just want to comment, Karen, the reason for this is really related to the fact that we amended these studies late. 83973 was amended, like, within six weeks of closing, or so. The 32 study only accrues 40 patients a year so we are capturing the majority of those. Once the new COG high-risk study opens it will capture a lot of patients, and this is not

an amendment; it is part of the study--

DR. MATTHAY: Right.

DR. REYNOLDS: --and I think we will get the samples. It is just that right now we are not but I think we will.

DR. DAGHER: Just two questions, one follow-up on the results of 3891, were there any exploratory analyses done to look at any relationship between the MYCN amplification status and the outcome vis-a-vis retinoic acid added to BMT? That is one.

The second one is there has been now discussion or mention of the newer study that is ongoing. I assume that study is building on the findings from 3891 so if you could briefly also describe the basic design of that study in terms of the arms and the primary endpoint.

DR. MATTHAY: Sure. In terms of MYCN amplification, overall in the whole study it continues to be a very significant prognostic factor for outcome. Interestingly, within the treatment groups it is not prognostic. So, it

appears, and this has been seen by the other cooperative groups as well, that once you move to myeloablative therapy you actually wipe out the significance of MYCN as a prognostic factor.

The current high-risk study is building on this study in several ways. We are using a more intensive induction because about 18 percent of patients progressed during the induction of chemotherapy on the study I presented. That was also based on some pilot data from Sloan-Kettering suggesting a better response rate. So, on the 3973 study which just closed we had the Sloan-Kettering type more aggressive induction therapy, and we switched to stem cells rather than bone marrow because of more rapid engraftment and ease of collection, and we showed that we could collect these stem cells after only two cycles of induction and that they would be clear of detectable tumor cells by a very sensitive immunocytology method.

We also did a randomization on that study to see if the purging was necessary because everyone on the 3891 study had purging. We have

actually had an accelerated analysis mandated by our data monitoring committee and that showed that purging did not impact on the event-free survival on this study, which is kind of good news in terms of making life a little bit easier and cheaper.

We also, on that study, were able to delete total body radiation based on another pilot study done outside the group that showed you could get in more chemotherapy if you eliminated TBI. You would then lose the long-term detrimental effects on growth and hormonal function and second malignancies.

So, that study is completed and we are awaiting the final analyses and survival data. Meanwhile, we did another pilot to further change the induction to try to reduce the toxicity and add a drug that had only previously been employed in relapse for neuroblastoma but seems to have a very good response rate, and that is topotecan. Based on some St. Jude's data and some COG data, we have a new induction regimen with two cycles of topotecan and cytoxan and then followed by four

cycles of the standard chemotherapy. On the new study, which is about to open, the randomization will be to test further the concept of consolidation they and whether that improves outcome. So, that study will randomize one transplant versus tandem transplant.

The other ongoing question for MRD that Pat alluded to is that our open study is now trying to improve on the data from the 13-cis-retinoic acid by adding an anti-GD2 chimeric monoclonal antibody with additional cytokines to stimulate the immune system so patients are randomized to receive 13-cis-retinoic acid alone or antibody with cytokines. The reason we don't just add it to everybody since the outcome is still below 50 percent is that the antibody cytokine therapy is very intensive. It requires monthly hospitalization and it has a lot of unpleasant side effects, hypotension, fever and allergic reactions and pain, and the antibody is not yet FDA approved. In fact, I am not sure there is any close prospect of it being approved. So, we wanted to really see

if it was worthwhile and this would be a registration study if that is successful.

DR. SANTANA: Kate, within the context of this new study that you just briefly described, what questions potentially could be asked about retinoic acid within the current study without having to write a new study or a new protocol?

DR. MATTHAY: I think one question is the one discussed, correlating pharmacokinetics with outcome. That is a very important question. The other question that you could potentially introduce, and I don't know if it would have to be done as a pilot, would be if you had a new formulation. You probably wouldn't want to introduce that into the randomized study but I think that is something that could be done concomitantly or we have some other high-risk pilots going on that are smaller where we could look at the new formulation. We have a high-risk pilot study that is going to run concomitantly with the new group-wide study where we are testing I-131 MIBG with chemotherapy for consolidation, so

targeted radiotherapy.

DR. SANTANA: And within that study are samples prospectively being collected for PG and for some future question? Or, the study currently as it exists does not allow for PG sampling?

DR. MATTHAY: Pat?

DR. REYNOLDS: Pat Reynolds. Let me comment on that. In the 0032 study, the antibody study, we are collecting a plasma sample and the pellet of the red cells which is enough DNA for the pharmacogenomics question. That is built into the next high-risk study for COG so that all of those data will be able to be correlated by the COG with outcome. The pharmacogenomics is not being done right now but the cells for DNA and the DNA will be made and it will be banked so you will have both steady state plasma levels on all these patients and the PG data available as the study completes.

DR. SANTANA: Can I follow-up on that? So, what are the important PG questions for retinoids that we should be asking?

DR. REYNOLDS: Gareth Veal has proposed

that some of the p450 system is going to be involved in metabolism of this. Some of the differences in generic expression of that could be related to metabolism of the 13-cis. We don't know at this point when a child has lower levels or higher than expected levels whether it is because of administration, as you said, within different foods, simply bioavailability and administration issues, or if it is a metabolism issue. So, we are collecting as much data as we can in the context of this about how it is administered. We have the plasma level. Then the idea was to ask the right pharmacogenomic question at that time. But right now we are banking the material so that that can be asked when the question is appropriate. I don't think we have enough data to ask it at this time.

DR. WINICK: If there was another formulation, is it conceivable that you could have a child who is in month five or four of the standard preparation for a defined period of time take the other, and do comparative PK? Would that be a more efficient way to study another

formulation? And, have a crossover design where you have PK on both?

DR. LINK: Yes, but you would have two IND agents on the same study, which I don't think would be a good idea. In the current randomized study, the 1418 is an agent that is being tested.

DR. MATTHAY: Yes, it would probably not be feasible to do it within the context of the current study, but I think there are enough pilots that we could do it quite easily. It could also be a separate study for people who aren't on any study but who are going to have high-risk neuroblastoma and take routine 13-cis, and there are plenty of institutions not participating in any of these studies who might do that.

DR. LINK: Or one of the other pilots.

DR. MATTHAY: Yes.

DR. SCHWARTZ: I was looking at the curve that had the overall survival, looking, probably not statistically, but at least other curves that the importance of cis-retinoic acid was in the BMT patients, at least for overall survival. Is there

something that we know of related to metabolism that is influenced by having gone through a transplant-Brenal, hepatic function, things like that, that have been looked at?

DR. MATTHAY: I suppose there could be but, to me, the logical answer is just that they have less residual disease, less minimal residual disease and that the retinoic acid is more effective in that setting.

MR. HUTCHISON: Dr. Matthay, this is my last question. I know there is an open COG trial, like SAHA. I think it is SAHA and cis-retinoic acid. I know Children's Boston has done some research on valproic acid and ATRA. Do you have any thoughts, or let's say you guys generate this Written Request, would you run this as a single agent or would you run it in combination?

DR. MATTHAY: The COG trial, at least that I am aware of, I think is mainly for brain tumors, the SAHA plus cis-retinoic acid. I think, again, when you are testing a new formulation we all get inpatient and we want to move forward as quickly as

we can, especially when you have sick children. But if we don't study things in the right way and learn about them, we are not going to get the answers and I think it makes more sense to study this in the setting of kids in complete remission and test the PKs with a new formulation first.

MR. HUTCHISON: [Off microphone; inaudible].

DR. MATTHAY: No, we would do it for children who weren't on another study or who were on a pilot study, looking at something during transplant and then they would go and take retinoic acid afterwards, or patients who didn't want to participate in the ANBL0032 study. I think, you know, the combinations are certainly very interesting and definitely need to be looked at.

DR. LINK: Ramzi, last question?

DR. DAGHER: Is the dose and schedule of 13-cis-retinoic acid that is being used in, as I will call them, post 3891 studies that you described, are they similar to what was used in 3891?

DR. MATTHAY: They are identical.

DR. LINK: A ten-minute break and then we will come back and have our public session and then deal with the questions about this retinoic acid issue. Thanks, Kate.

[Brief recess]

Open Public Hearing

DR. LINK: The next item on the agenda is the open public hearing and I will read our statement in anticipation that there may or may not be somebody in the audience who would like to address this group:

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial

relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include a company's or group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Let me just ask if there is anybody in the audience who would like to address the committee. I assume that the answer is no.

Questions to the Pediatric Oncology Subcommittee and Discussion

So, I would like to continue with the next item on the agenda, which is actually the questions that have been assigned to the Pediatric Subcommittee for discussion, also printed on the page after the agenda. It says two questions:

Given the results of the Phase 3 randomized, controlled trial in high-risk neuroblastoma patients who received intensive chemotherapy, radiotherapy, autologous stem cell transplant and 13-cis-retinoic acid, should the FDA ask for submission of these data as a supplemental NDA to potentially support a new indication?

And, please discuss other types of studies or data that should be part of a Written Request to further inform the safety, dosing, and efficacy of 13-cis-retinoic acid in pediatric patients with high-risk neuroblastoma.

It was suggested to me, and I think it is a good idea, that perhaps one of the FDA members of the committee inform us a little bit about what is required for a supplemental NDA. In other words, what is the gist of that; how detailed does it have to be, etc.?

DR. WEISS: Generally-Byes, Rick's comment was it varies. It varies, but generally if we are talking about a new indication for an already approved drug, usually the situation is it is a

drug that is already approved for one oncology indication so it is not that much of a leap of faith, if you will, to extrapolate maybe findings from one tumor type to another tumor type. But generally it requires data, usually a controlled trial, to establish that the drug's effect. Usually there is not as much of a need for as much safety information unless you are going from, like, a metastatic setting to maybe, like, the adjuvant setting where you might have a different risk/benefit ratio.

So, you know, there is no one size fits all. It really depends on what your priors are. In this case, if we are talking about a supplemental NDA for 13-cis-retinoic acid, we are talking about the indications that is on the market right now is the drug everyone knows as Accutane for the treatment of the dermatologic condition and it is used, you know, obviously in a very healthy population and there is lots of information already, safety information. Dosing may be a little bit different, and the regimen, etc., is

different in terms of duration, etc. But basically if you want to if you want to support a new efficacy indication you need sufficient information to establish that the drug is effective, and in that information you need to safety information to be able to write an informative label.

DR. LINK: So, with that sort of background, Jerry, since you did the first study of this maybe you would like to lead off the discussion.

DR. WEISS: And let me just clarify. I mean, you know, the idea is we would ask for the submission and we would review it. We obviously have what Dr. Matthay presented in terms of the 3891 trial that was published and you have in your background, published in the New England Journal of Medicine, but as you heard earlier this morning, we generally do not rely on literature. We actually rely on looking at data. Anne Zajicek is back in the audience. You certainly can come to the table and you might want to do that. But if we issue a Written Request part of the job that might be for

the Foundation or NICHD is to actually put together a submission for an application for the agency, you know, to go back and collect some of the primary data, to go through the CCG records to actually put together something in a submission that was something that the FDA could review.

DR. LINK: Malcolm?

DR. SMITH: I have just one detail for Kate. The primary analysis was log rank or the test of proportions?

DR. MATTHAY: The primary analysis-the study was designed to use the test of proportions because Dan Stram, who was the statistician, actually suspected that we were going to be in this situation of crossing of the curves. However, when a new statistician re-analyzed all the follow-up data she said, oh, we should do only Kaplan-Meier. But then when we looked at the curves again she saw that in the cases where that was violated she needed to go back and do the test of proportions.

DR. PAZDUR: So, the protocol pre-specified analysis was the endpoint-

DR. MATTHAY: EFS at three years.

DR. PAZDUR: At three years was the proportion analysis.

DR. MATTHAY: Yes.

DR. SMITH: And that was positive at three years for both EFS as well as for survival?

DR. MATTHAY: No, only for EFS in the initial analysis.

DR. SMITH: And the test for proportions at five years--

DR. MATTHAY: Was significant for survival. That manuscript is about to be submitted. Can I ask a question? I was just involved in another drug company that wants to get their drug certified from some old CCG data, and to do that they are going back and auditing primary records of patients from 15 years ago. My question is I know that all this data, which I presented the summary of today, is somewhere at CCG on computers and in the database and also on paper data forms because we did not have our DE. But would you foresee that the FDA would require somebody to go back and audit

the primary sites?

DR. LINK: I think one of the issues there is lack of follow-up. I mean, it was a different issue in that study than might be presented in a neuroblastoma study.

DR. WEISS: It is a possibility. Whether or not it is actually definite about going back and auditing primary site data, you know, it might depend also to some extent on what is seen if a submission comes together and starts to be reviewed, and there start to be questions about certain things that are just inconsistent. We don't always audit, particularly if we are talking about supplemental indications. We don't always audit, go out and do specific audits of sites. Anne, do you want to comment a little bit on just what might be envisioned in terms of putting a submission together if, you know, the NIH or the Foundation was involved in this?

DR. ZAJICEK: Sure. Well, I must first of all thank Malcolm Smith for making this possible because there is no way this could be done without

him. So, thank you. Anyway, the trajectory here is that we would discuss what data set it would be and where it is. Then the question would be who would physically go in and look at the data. So, for the vincristine-actinomycin-D, you know, funds have been transferred to NCI, to COG to have people who know how to look at these medical records, because you can't have anybody going in there and looking at them. It has to be an oncologist or oncology nurse or somebody that knows what they are looking at to make a record of exactly what it is you want.

For example, vincristine demographics, dosage regimen, toxicity, however it was recorded, that kind of thing. So, we would need to figure out what would be on our case report form, exactly what we would need for the submission. Then somebody would go in there and look at whatever paper trail there is of the data. Then, at the end of that, there would probably be some internal audit at some point about some of that data to make sure that it is looking like it should look, like

what is in the case report form, what is in the primary data, as we do with the other BPCA trials to make sure that the data-Bnot that somebody is creating it but, you know, that it is consistent and that it relates to the primary data set. So, that would be for the paper audit stuff.

We have a coordinating center that deals with all the BPCA trials. So, the plan there would be for them to put some sort of package together for you guys that would fulfill the requirements of the supplemental NDA as far as, you know, efficacy, how we are evaluating efficacy, data tables explaining the efficacy, the endpoints, the toxicity, and so on. Then that would be in as a supplemental NDA package, at least for this part. Not the PK but the efficacy.

DR. MATHIS: The other part of the process is that for the off-patent Written Requests the information does come in. It gets submitted into a docket, and then we have worked out a process internally, which has not been tested yet because we haven't had any data for the off-patent process

come in yet, but we do have a process laid out for how we would get information from the public docket into labeling. So, it is on paper. It hasn't been tested, like I said before, but the submission process is a little bit different for the off-patent process and NIH does have a coordinating center that would put together the data so it would look like it came from a drug company, or whatever. But then it would have to be processes from a public docket.

DR. ZAJICEK: Which is nice so the data would be available publicly in some form so it wouldn't be coming in directly from us to the FDA. I mean, it would be available to outside people as well.

DR. PAZDUR: I just want to remind people that just asking for a Written Request does not mean necessarily that we would approve this indication. That is point number one.

Point number two, before we get caught up in this whole issue I just want to ask people--and I think this is one of the reasons we wanted this

discussion because this would require a substantial amount of work and expenditure both of time, energy and money, federal moneyB-do people think that having this in the label would be of that benefit of bringing all of this data in. Here, again, you know, I have no idea whether we would approve this or not. I am not going to be making a commitment based on a presentation here for an approval. There could be a lot of problems that one sees in cooperative group data, etc. Is the issue here one that would warrant that expenditure of time and money, and for what reason?

Obviously, you know, we put things into the label to inform practicing physicians of the results of this trial. If we were talking about a drug in the general population, you know, outside of pediatrics or even in general pediatrics that might be a consideration. But let's face it, the people that are treating this disease are a relatively tight group of people that have a great deal of expertise in this field. So, to say that we are putting this into the product label to

inform practitioners, you know, they pretty much would know about this, I would hope, and if they don't know about it they probably shouldn't be treating these people.

DR. LINK: This came up maybe before you came right at the beginning of the meeting. That was the first question that was asked. So, you know, everybody knows this. I mean, I think more people read the New England Journal of Medicine than read the package insert. So, we know this stuff and as far as life changes, or what was the word?B-you know life changes anyway so we have this updated data.

But one of the interesting sort of add-ons that was mentioned as a possibility is could this be used as a way of getting a more suitable formulation for children? In other words, as part of the supplemental NDA application could there be a request for a better formulation or something like that? Because that would be worth it to us.

I think I would ask the question a different way. That is, without doing something

sexy do we care? Do the people around this table who treat the patients need this? And, I think that most of the pediatricians would say the answer is no. I mean, it is part of our routine care of these patients. It is already accepted as the standard. But sort of the question is what could we do with this to enable us to do something that would really be of value added? You could ask the group. I think that would be one of the most important things.

DR. PAZDUR: But that really is a different issue.

DR. LINK: Yes, but the question is, asking it the other way, if you didn't do that, I think most of us would say spend the moneyB-well, even our patient advocate, you were the one that suggested it, spend the money on something more useful.

MR. HUTCHISON: Well, no. I like the idea of a new formulation because that is important for our children. I think that is really critical. But also I think answering the question of the PK

is important too because, I mean, we are prescribing this drug to children in remission and we don't know what PK they are achieving.

DR. LINK: But there is a study open to get that information. In other words, we don't need this process to get what you are interested in.

MR. HUTCHISON: Okay, I will tell you what I am really interested in, and I don't know if you could ever do this, but I wish coming from this meeting, or some meeting, there would be a written communication telling, you know, for children on Accutane right now, go get your PKs measured or something to see if you are getting the adequate dose. Because, I mean, you have the scientific aspect; my perspective is the saving lives aspect. I know you guys are into that too but, for me, I would violate all federal regulations if I could but, you know, you have kids out there getting this drug today and we can answer that question right now-Bgo get your PK measured; you know, go get tested for HIV; go get your PK for Accutane measured and answer that question. If it is not

suitable, then--

And, you can even answer the formulation question. Let's say we don't reformulate it and you still do what Dr. Reynolds said, you squeeze it into applesauce and give the kids applesauce; you get your PK levels measured and your PK level is low. Well, the next time you double the amount of stuff you squeeze into the applesauce. You know, so maybe you can get the PK levels for those children at the acceptable levels anyway. Because really what we are after is not a new formulation. We are after a PK level and a new formulation is a way to get there.

DR. LINK: There is a little science we have to do there. We have to prove that the level that you achieve is relevant in vivo in patients. So, I mean, that would be a piece of work and probably more than anybody would be willing to commit to on a supplemental NDA. It is a whole huge Phase 3 trial you are talking about.

DR. FINKELSTEIN: I would like to answer Richard's question. The answer in my opinion is

no. I think you could argue about the relative value of 13-cis-retinoic acid in terms of long-term survival. In terms of tumor maturation, that is a phenomenally important concept. Whether this drug will be the ultimate of tumor maturation, I think most of us hope that it isn't and there is some other pharmaceutical coming down the line that will show such dramatic changes in curves that we don't have to argue about the statistical method and when the event-free survival occurred from randomization, from intent-to-treat. I mean, there are a lot of things you can dissect regarding this study and, rather than spend the effort to dissect, I would rather we put the effort somewhere else because those of us that are using it, for better or worse, know how to use it and, hopefully I am optimistic enough to say that somewhere down the line there will be some real agent that we need our efforts for.

DR. SANTANA: Jerry, let me see if I follow you because there are two questions here. The first one is whether there should be an effort to

collect the data that already exist in a way that can be formulated into supplemental NDA for a new pediatric indication. That is one question. I think I have heard different reasons pro and con of whether we should invest our money, right, because we are all taxpayers, in doing this. That is one question.

The second question, which is totally independent but it could be linked if you go down this route but it could be a separate question, is what additional information should we request on this drug? So, whether there is a supplemental indication or not is not the issue. The issue is it is being used right now by people on protocol and off protocol. What additional questions can we ask that would be relevant to help our patients?

Those two questions are not tied. So, if you disagree with number one, that is your opinion but I don't think we should just automatically deduct from that that question number two is not relevant. Is that what you are saying?

DR. FINKELSTEIN: Well, I think you are

excellent and you should be my attorney at all times and express what I am trying to say. I agree, then the question is who takes on the second question? And, is that the role of the FDA or is that the role for those of us on the front line doing this, either through Malcolm through the NCI or through COG? I interpret this as saying I didn't think this was within the role of the FDA necessarily but it certainly is a question that requires an answer.

DR. LINK: I thought you were only talking about question number one.

DR. SANTANA: So, are number one and number two linked in terms of can we have a Written Request for an oncologic indication for an acne drug?

DR. WEISS: Well, you could have the Written Request. I am trying to think though. See, you know, if you use the logic though that, well, this is a kind of a captive community of oncologists and you all work together and share information, and it is a small world and you all

know things, then you could argue, well, what is the point of getting any of these drugs studied as part of BPCA on- or off-patent process because, you know, you just know the information and, if nobody cares about the label anyway, then why? But you could make that argument that it is information that will be shared, will be known. It is not like, you know, the doctors out there in the community that need to have specific information. You could almost make that argument about all the discussions we have had over the last year or so on a number of other drugs, both on-patent and off-patent.

DR. LINK: Karen, I disagree with you on that and that is that there is a specificB-we are not looking, for example, at actinomycin-D and vincristine. We are looking for a supplemental NDA. We are looking for finding out a specific issue related to VOD or neurotoxicity in vincristine which we want answered. We don't want to know that it is efficacious in leukemia. I mean, there is a boatload of papers on it. Here,

the first question at least, let's look at that, is asking do we want a supplemental NDA that says that this stuff works in neuroblastoma? I know that. My fellows know that. They read the literature, hopefully, and they certainly read the literature that has been published this prominently.

So, I guess I misconstrued the linkage. I thought that I would do number one if I could get the hook of number two into number one. That is what I was suggesting. But I don't want to do number one just for that. I wouldn't do it for the sake of doing it. That is what I thought Jerry was saying too but I misinterpreted it.

DR. WEISS: But I guess the question would be-Byou know, somebody suggested maybe we should turn around and address question two first because it sounds like there is lots of very important information. But I guess I am trying to reason it through. Let's say we went to two and said, you know, there is good pharmacogenomics and pharmacokinetic data and formulation issues that are all really important that should be part of a

Written Request. But then how would that go into a label for acne, I mean for a drug that is only indicated for acne? It wouldn't. You would somehow have toB-it seems like they are sort of tied in a way, especially if you all think it is important to get information on PK and formulations into a label because it is an important question to answer, then you kind of need, it seems like in my mind at least, a place in the label to put it that is relevant. And, is it relevant in the information on acne?

DR. PAZDUR: Perhaps you could even put it in other places in the label, for example pediatric section, warnings section, other areas depending on where it would be.

DR. MATHIS: Please remember that tamoxifen was studied for McCune-Albright syndrome. It did not get the indication but there is information from that study under the pediatric use section of labeling. While I appreciate the fact that you all don't read labels--

[Laughter]

-BI think it is important to remember that the mechanism that we have under BPCA is to issue a Written Request and then NIH can fund studies for information that is lacking. So, we issue the Written Request. We fund the studies that are needed and we get that information into the public domain, which is what you guys do read, and then we figure out how to get into labeling.

DR. LINK: But I think this question we know the answer to. So, we don't need more information about the efficacy. We need more information about something else, and if that is what it takes to get the other information then I think, you know, we can discuss it.

DR. WEISS: I guess my question though is if we know about the efficacy is it important to have that information in a label, and because this is a drug that is not like vincristine and actinomycin and methotrexate and it does not have an oncology indication currently, is it important to have that indication in the label even though you all know about it? And, the way to do that

then would then require basically NIH to pull together a submission, meaning going through records, creating data sets, etc. to submit to the agency because there isn't going to be a company that is going to be putting in their resources to do that at this point.

DR. PAZDUR: But I think what Lisa and I were trying to say was that, you know, you all believe, from your previous comments, that this is a well recognized issue in pediatric oncology, the existence of this trial. You really don't need it in labeling to educate people. Future studies that would need to be done and the resources to do those studies could perhaps do the studies and then information could go into other parts of the label, such as the pediatric section, if there was a need for warning or interactions with drugs and other issues could go into other parts of the label without the indication. That is why I was asking the fundamental question, what is the value to you, not to us but to you to have this information in the label on this study? It isn't the hook here

because the hook could be in other parts of the label necessarily.

DR. SMITH: I was just going to ask if there are others who would like to speak on why this should be in the label. Is there sentiment from others around the table that would argue that this should be in the label, and why?

DR. PAZDUR: Remember, this is a double-edged sword. It could be reviewed and then the quality of the submission is not sufficient for it to go into the label. Then that poses a problem.

DR. WINICK: I am sorry, I am not trying to be dense. It is or is not mandatory to ask for the supplemental indication to fund PK, PG?

DR. PAZDUR: It is not mandatory.

DR. DAGHER: Could I clarify? I assume, Malcolm, that your question is phrased in the context of wanting to get input on whether it is important to have this in the label as an indication. Is that what you were asking?

DR. SMITH: Right. That was the question,

as an indication or does anyone want to speak on the advantages of spending time and effort, resources, not COG resources--I mean, you know, this would be BPCA monies, our money--to get this information and have an indication for this in the label? That was the question.

DR. SCHWARTZ: I guess sort of where Naomi was going and maybe naively looking at this, it looked like the purpose of some of this was for us to better understand the drugs we use in the treatment of children with cancer and, therefore, to have a mechanism that gets us that information, PKs or toxicities, and why we are getting them and things like that. So, I think that to me, as an oncologist, yes, we all know that we use this and it works, but hearing the data, it seems like we really do need to understand better which kids get the right levels and how we get the right levels, and what goes into that. So, again, I don't care whether it is in the blurb but it seems like there is something about this drug that we are using routinely that we don't understand and our children

relapse because we don't use it properly, whether we need better ways for administering it; whether we need to know that kids who have problems with absorption or problems with their creatinine, or problems with the livers are the ones who need higher doses, kind of different than what we are used to. Are kids metabolizing too fast? We need to understand that. That is important as an oncologist.

DR. LINK: So, there are a couple of questions. Number one, the first thing then is not related to what you just said. The first question is whether we should take the data from the trial that we just heard presented by Kate and submit it to the FDA and say that is a reason to give this drug, that it is indicated for the use of treating kids with neuroblastoma status post bone marrow transplantation or status post intensive chemotherapy.

DR. SCHWARTZ: That would only be if FDA needed that to be willing to do the second part.

DR. LINK: Well, you are tied with where I