am so we have to untangle this. So, let me ask another question to the NIH people. Why was this drug stuck on the list as a priority drug? In other words, what were the issues that NIH wanted to know to put this on the list of drugs that should be high priority to study that was off-patent?

DR. ZAJICEK: This was proposed by the COG and in particular by Pat Reynolds. Comments?

DR. REYNOLDS: Pat Reynolds. There were a number of reasons why, after discussion with the neuroblastoma committee, we felt that this would be a drug that we would want to bring in front of the BPCA to be considered, which I did last fall at Karen's invitation and everyone felt that it should be. One of the reasons wasB-and with all due respect to you not reading the labels, insurance companies do read labels and a lot of parents end up having to pay for this drug out of pocket because it is not indicated.

DR. LINK: Is that true?

DR. REYNOLDS: I know personally it is

true. The second issue is that without an indication we are always stuck with this being an acne drug and I think that there are some issues with access to this drug that we should probably discuss at another time but that are really important to consider in the context of whether or not a labeling change would help the pediatric oncologists in terms of their accessing this drug to treat their patients.

The third reason is that it was my understanding, and perhaps naively, that the whole point of the BPCA process was to centralize the information related to drugs used to treat children in the label because that is the primary regulatory oversight. The label is what the FDA oversees in terms of what is real and what is Memorex. Although the New England Journal is certainly a very, very prestigious publication, it is not the FDA. And, I think people really look to the Food and Drug agency for this sort of information and the absence of it, I think, for a drug that, as John Morris [?] recently described in an email is

one of the few drugs we have seen in a randomized trial that actually benefits children, is a glaring absence, in my opinion, from the label.

I think that there are also a lot of long-term follow-up data that could be obtained in the context of getting this. The cooperative group is not positioned to do that. As everyone noticed the decrease in resources available to the NIH, there are simply not enough resources for the cooperative group to go do this. Through the BPCA mechanism, that would be one process to go back and get these data.

Finally, as we mentioned, there are foreign access issues for patients that would be facilitated. Richard is shaking his head but the fact is that this would benefit them and I think it is worth recognizing that there would be a benefit. It is not our responsibility but it would be a benefit.

DR. LINK: Could I just interrupt you one minute here? In terms of reimbursement, there are many drugs that are given off-label that are in the

compendium and if the compendium lists this, which is usually based on peer review manuscripts and not based on labeling, so if it is in there-certainly that applies to CMS and it also through CMS applies to everybody else. This is a reimbursable drug because the data are out there in the literature. I mean, I guess we could check the compendium but I can't believe it is not in there as an indication.

DR. REYNOLDS: Mike, the problem here is that we are talking about a non-antineoplastic agent used as an antineoplastic agent, and there is no indication at all in the label for treating patients in the oncology setting with this drug unless they have acne. So, I know that there have been issues with reimbursement. Now, certainly there are plenty of cases where there have not but I think it is an issue.

DR. WINICK: Again, going back to question one versus question two, if BPCA funds are used to address very important clinically relevant questions with respect to the use of cis-retinoic acid, and if there is a place in the label to put

it, with respect to Pat's concerns about reimbursement, drug companies, insurance companies, etc., etc. and education, isn't one allowed to make an assumption that if there are comments on what plasma level you need to achieve in the treatment of neuroblastoma using cis-retinoic acid that there is an implicit labeling?

DR. WEISS: Potentially it wouldn't be specifically an indication statement but if it is elsewhere in the label many would consider that to be an implied claim. I have no idea whether or not reimbursement-it would seem logical-you know, I don't know how that would be handled with reimbursement because we don't deal with that, of course, at all. I mean, I think the important thing is if there are important studies that should be done that would further the field, then we need to discuss what those are and how to do them. Then, as Lisa said, we figure out how to disseminate that information. Our way to disseminate things is through the prescribing information in the label. I really am surprised.

I didn't think the question was going to create such controversy as it has.

DR. LINK: It is because you are talking about our money. Why don't we reorder the questions? Can we do that?

DR. WEISS: Let's do that.

DR. LINK: Let's do question number two and then maybe question number one will fall out--

DR. WEISS: Sure.

DR. FINKELSTEIN: Michael, I have a suggestion. The problem was I was answering question one with two questions and I never got to question two, but getting back to it, Richard missed this morning where we actually agreed as pediatric oncologists, I think, that the label is important because the public reads it. On the other hand, since the label is owned by the drug companyB-we learned that this morning, and since at least I have voiced an opinion that I don't think we should put our money, our resources into this kind of study though I think we need other studies, my question is would not the FDA and the drug

company agree to some statement in the label indicating that this is being investigated as a potential drug for pediatric cancer? That would solve the problem.

DR. LINK: The drug company would love it.

DR. DAGHER: Well, the difference between this morning's discussion and this-BI guess you already got your answer.

DR. WEISS: I was going to say there is really not much interest in the pharmaceutical companies. In general, the pharmaceutical companies don't get any financial advantage to having a pediatric oncology indication or explicit indication in their labels. There is just no money in that. And, there really was an interest before this drug went off-patent to do some additional studies to pursue this as part of the BPCA on-patent process.

DR. DAGHER: I agree. The distinction I was trying to make, aside from the initial issue, is that once you are in the off-patent realm it is evenB-how shall I say?-Bthere is even less of an

incentive there.

DR. LINK: I would like to take the prerogative of looking at question number two and then we will discuss question number two independent of question number one, trying to unravel them, and see if there is any benefit to raveling them if we think that number two is important and then we can talk to the FNIH or the NIH representatives about what needs to be done, and the FDA.

DR. MORTIMER: I have concern that there is a negative trial in Europe, and it may very well be that it is 15 percent of the dose, and so on, but I think you have to prove that. The other component is that, and maybe this isn't true in the pediatric world as opposed to the adult world, but I can't imagine that somebody wouldn't cut the dose because of side effects and who knows low long you are supposed to treat these kids for? So, you know, maybe 34 months is too short but, I mean, at least 34 months should be said somewhere so that people know.

DR. LINK: Six months.

DR. MORTIMER: I am sorry, six months, 34 weeks.

DR. LINK: I am not sure, you are sort of talking about item number two now.

DR. MORTIMER: Item two, yes. I mean, it bothers me that there is a negative trial in Europe. While it makes a ton of sense that it is a low dose, you don't know that.

DR. LINK: The medical oncology colleagues are telling us that this is great.

DR. RICHARDSON: I am really glad that Joanne mentioned that because I am sitting here, looking at these four curves, the last slide here, with the overall survival from the time of the second randomization, and if you look at the bottom three, all three of these overlapped in my mind. So, we got one outlier. We got a negative study. And, one of the referencesB-Dr. SCHWARTZ and I were talking about this earlier, one of the references from one of the papers was a reference by Seeger, from 1991. It talks about the risk of relapse in

high-risk neuroblastoma patients as being 50 percent.

These numbers aren't that much different even in the best arm. So, where are we going with this thing? I mean, how much stock do we put in these numbers? We are doing this on the basis of one study.

DR. WEISS: You know, in the field of pediatric oncology, I mean, this was I think by many standards a very large trial. Because it included the two randomization arms you end up having relatively small numbers. You have your event-free survival outcome which certainly looked impressive. You have, you know, numerical differences in overall survival, even though perhaps because of the small numbers, etc. you don't maybe have the levels of significance you want. So, yes, it is a question. You are right. You know, maybe the question should be should there be more studies that are done. I mean, I think it is a good segue into trying to really get some specific input from you folks on issue two. What

other studies, what studies, what types of studies should be part of a Written Request? You know, it is on the priority list. If you all think it is appropriate for the agency to issue a Written Request, it could be a number of different types of studies. You know, we have all talked a lot about PK, formulations, etc. But, you know, we put everything on here. You know, do we need safety, dosing, formulations, efficacy studies? What do you think? What could the field use in this disease?

DR. LINK: Sort of back to the issue of if they submitted this supplemental NDA with that data you would probably vote it down and they wouldn't get it approved. So.

DR. DAGHER: Just to focus a little bit more, you know, Dr. Villablanca [sic] and Pat presented some preclinical and PK data. Dr. Villablanca presented some early studies, dose-finding studies, in addition to a completed randomized trial, in addition to a question and answer componentB-Dr. Matthay, sorry-Band, you

know, described the basic design of at least one study that completed enrollment and additional studies that are either ongoing or are being designed.

So, I guess taking all that into consideration, let's say we, for whatever reason, have decided or not that the results from 3891 would or wouldn't be submitted regardless whether it is for an NDA or simply as part of a Written Request, aside from the results of 3891, we have all these other studies that are either completed, ongoing or planned. Of those, what do you think would be the ones that might help inform the field as Dr. Weiss was saying? Maybe that helps.

DR. WINICK: I mean, to me this seems almost perfect in that what Kate suggested, what Pat suggested is that the role for this drug is in a setting of MRD. And, when 3891 was done, and Kate should correct me if I am wrong, tools like MIBG, etc. were not available to assess disease status. It could be that it is less effective in the population as a whole but impressively

effective in sort of the right population. So, if PK studies were done, if you could determine in the current era who really is at a level of MRD versus who still has microscopic disease you might accomplish some of the goals of the BPCA. You would gather more clinically relevant information and then that could provide if, number one it is important, the data you need for the new indication.

DR. LINK: My sense of question two is that we thought of a number of things that need to be done. I didn't even see here about the formulation thing which, you know, again comes up that needs to be done. I think we should get a sense of the group as to should we be working on question two for all the reasons that I have heard, that we need to correlate serum levels with outcome; that we need a new preparation. Is that worth doing? And, why don't we vote on that and then we can sort of decide what is next. Oh, we don't vote. I am sorry. Get a sense of the room? We are not allowed to do that either?

DR. WEISS: That is good.

DR. LINK: Sense of the room.

MR. HUTCHISON: Can I ask one question? What does this crowd out? If we do this, what does it preclude us from doing financially, or funding-wise or anything like that? Because, as a parent, does that make any sense to anybody?

DR. LINK: [Off microphone; inaudible].

DR. ZAJICEK: Sure. Just to give you the funding outline, the Best Pharmaceuticals for Children Act is implemented at the NICHD by the NIH, not the Foundation but the NIH. That is something else, so the NIH. So, the way this is funded is that there is a tap on various institutes, not centers but institutes at the NIH in proportion to how much pediatric research they do. There is a total of 25 million dollars on the table per year to fund BPCA. Seven comes from NICHD, the Institute I am with, Child Health, and then the rest of it comes from various other institutes, NIMH, NCI, NHLBI and so on. The only think on deck at the moment for oncology is this

project. So, if you decide not to do this project it is not as if there is another cancer project on deck at the moment for BPCA.

MR. HUTCHISON: And do you have any sense for what this would be budgeted at? Is this like a two million dollar project, one million dollar?

DR. ZAJICEK: You know, I don't know. I do not know.

MR. HUTCHISON: How about the average of your other Written Requests? Would you be able to use that as a ballpark?

DR. ZAJICEK: I can tell you thatB-well, it depends. We have projects funded by the contract mechanism, as I said this morning and then the cooperative agreements. So, I would ballpark it at maybe ten million dollars for one of the contract studies. So, lorazepam for status epilepticus, status sedation, those kinds of things is somewhere in the ballpark, not per year but total of how much those studies have cost. The other studies that we are funding have varied a lot so I don't really have a ballpark of what this would cost. I mean,

the cost would be, you know, data accrual, going into the case reports, perhaps funding or co-funding a PK study. Maybe. I mean, I don't know. I am just sort of stating sort of a blush here. Then our coordinating center putting together the data packets. So, there would be money going to the coordinating center and money to COG to fund this.

DR. SANTANA: So, Michael, although I want to be a good steward of the public monies, I don't think we should base any decision based on money. The first decision should be based on science. So, I am convinced that there are important questions about the use of retinoic acid that we can ask through this mechanism, and I am in favor of those. This drug is being used right now for children with neuroblastoma on protocol and off protocol. We all struggle with everything we have heard in the last hour in terms of what is the right dose, whether there is any relationship between exposure and response and toxicity, is there any pharmacogenomic marker that we should be using to

guide our therapy in these patients. All these are important questions. So, I hope that the discussion is not steering that this drug is not important and we should take it off the list because I think there is important science here that still needs discovery and this drug is being used today, and I think we have a responsibility to learn some more. So, I don't want to have a discussion based on money.

DR. LINK: I agree with that. We have heard a couple of comments now about, including for me so I concur also, that there is stuff that we need to know, and we have given you some ideas about what some of those things are, although I don't know how we would prioritize those individual things that we want to know but we certainly do want to know, and how attainable they are from data that already exist versus that new studies would have to be launched. So, is that something that people can rally around, that that aspect of this drug we do need to know?

DR. DAGHER: Could you summarize those

elements?

DR. LINK: Well, I think you heard it best from the last comment, that I think we are interested in pharmacokinetics; the correlation of levels with outcome. I mean, that is something that we would like to see; and efficacy. My pet thing is different formulations and their utility and how they compare with standard formulations both in terms of compliance, let's say, and achieving levels that you want. What else did you say that was good?

DR. SANTANA: Pharmacogenomics data.

DR. LINK: Oh, yes, and differences in pharmacogenomics and these metabolites. Some of this stuff may be available to study but we are waiting to study it. So, the issue may not be whether it is feasible to do the study, just whether we can write the right Request for it and fund it.

DR. FINKELSTEIN: Michael, I think we also need, in keeping with this comment, an outside detailed analysis of all the data available using

retinoic acid in neuroblastoma worldwide. In other words, one of these great objective analyses--

DR. LINK: A meta-analysis?

DR. FINKELSTEIN: Well, not meta but looking at the data to really see if we understand its efficacy in terms of statistics.

DR. LINK: Okay. That tacks on a big chunk of stuff to do. Cindy?

DR. SCHWARTZ: And using that, I think you do need to correlate it with various toxicities the kids may have had with renal toxicity, hepatic toxicity and things like that in terms of the drug.

DR. LINK: That would be part of a toxicity profile.

DR. SCHWARTZ: And how that correlates--

DR. LINK: Yes. So, I think you have a sense of how we feel about item number two that, you know, as the usual conclusion, more research is needed. Except for that last comment from Jerry, I didn't hear much about that we wanted to take the data from CCG, from their study, and try to get a supplemental NDA. So, can we go back to question

one?

DR. DAGHER: Can I push you a little more about two? I think to answer the part of the question which asked what are the important issues, I think that has been addressed very well. I have still a final attempt to push the issue of the studies that we heard about that are either completed, ongoing or planned, given the big list that we have discussed in terms of the issues, what would people say of those studies, which ones do you think would be important to include potentially in a Written Request letter? Let's say the budget issue was not a constraint.

DR. LINK: I don't know that I would prioritize. I think we each have our own sort of take on this. Anybody want to chime in here with what they think is most important?

DR. WINICK: You are asking about which of the studies that have already been competed?

DR. DAGHER: Not necessarily, either completed or ongoing--

DR. LINK: Are you talking about these

issues?

DR. DAGHER: See, you identified issues related to safety, dosing, formulation, toxicity, pharmacogenomics, etc. Some of the studies that have already been completed, are ongoing or planned might address those different aspects. Let's say at some point we make a decision that we are going to write a Written Request letter, regardless of whether it is going to lead to an NDA or not, we are going to have to decide what kind of studies to ask for, or results of studies. That could include studies that have been completed, some that are ongoing or others that are being planned. So, that is what we are tryingB-I know it is hard because there was a wide range of objectives in the different studies that were discussed but that is kind of the last piece I think of this question.

DR. WEISS: And that actually sounds to me-BI am not so sure, you know, that the folks that really have their fingers in all of the ongoing neuroblastoma 13-cis trialsB-you know, if this committee feels that there are studies that are

important to do, then we need to have some very significant discussions with our people that are sitting out there in the audience that have actually presented the data to find out the very specifics of those trials, what is ongoing, what has been done, what has been collected from those studies to figure out, you know, what makes sense in terms of issuing an aspect of the Written Request, what is feasible to do in terms of conduct of new trials because, as we heard from the discussions this morning, you know, there is the whole practicality and feasibility of studies. You know, we can ask for the sun and the moon but if they can't be done because of the prioritizations within COG, or whatever, then it doesn't make a lot of sense anyway.

So, if we get sort of marching orders from this committee that there are a number of important areas that you have already outlined, and I think you summarized them nicely, Mike, then probably the next stepB-we still have to get back to number one and we should do, if it is the last thing we do

maybe, but a step then would be to sit with the neuroblastoma experts, the cooperative groups and say, okay, these are the things that are important to consider; these are the studies that are either planned or completed; there are samples collected. How can we sort of marry up all of that information together to make, you know, a really appropriate Written Request that is doable and is going to answer the most important questions and will get us the answers we need.

DR. LINK: I am worried about the fact that the one that a lot of us may think it is important may not be encompassed in that list, and that is new formulation. So, there is nothing there in studies that have been done that is going to address that. And, I think we have heard from the people who are using it that there is real concern about how you deliver this stuff and so I am afraid that no studies have been done because, you know, if we had a study done we would have a new formulation. Again my prerogative, don't forget that one because that one that I think is the most

novel and may be most expensive.

DR. WEISS: It is the most novel but it is more difficult in the sense that there is no pharmaceutical company that is going to be backing it up so you have to determine who has the resources and the abilities to come up with that first of all before you can actually test it.

DR. LINK: Anybody have any further comments about what Karen just said?

DR. SMITH: Has this been done with formulations where there wasn't a company with other agents?

DR. ZAJICEK: Well, I would have to say no because the one formulation that we are using is the one for baclofen and the story with that one was that that formulation was developed through an SBIR, the Small Business Innovation Research, grant through the NIH, and they came up with a liquid baclofen formulation that was fine. So, they took that information and formed a company called Phase V which is now manufacturing the liquid baclofen. So, that is the trajectory of that. So, we haven't

made anything de novo exactly.

DR. SMITH: So, it is not to say we couldn't. We just don't have a well identified path for it.

DR. ZAJICEK: That is correct.

DR. WEISS: So, it is something I guess that, I mean, might require a little bit more homework to see if it is feasible. You know, we can put it in the Written Request but if there aren't any takers and we just don't have, you know, people that have the skills for making that, then, you know, it is just something that wouldn't be done.

DR. LINK: See, it worries me when we talk a lot about pharmacokinetics and we talk about people making drug dose modifications based on toxicity because they are winging it or because they think it is the right thing to do. We haven't even addressed probably the most difficult thing about this drug, which is their kid didn't take it and they are tired of fighting with their kid at dinnertime or after dinner at bedtime and so they

don't give a dose. And, that is probably going to have more impact on the level and pharmacokinetics than any of the things we have talked about that we may measure and have samples frozen for. Do you want us to address item one?

DR. WEISS: Well, I guess the question I have if you think about it this say, let's say that we, you know, look at these other aspects of 13-cis that people think are important and we converge with Drs. Reynolds, Matthay and Villablanca and the experts and ultimatelyB-it is going to be a bit of work, but articulate what would be aspects of a Written Request for these what I would call additional types of studies, you know, looking at the best way to optimize how to administer it, if you will. Would the committee think that information on thatB-because I hear some people's concerns that, you know, maybe this trial that was presented, 3891, maybe wouldn't cut it in terms of a potential new-Bmaybe it would, maybe it wouldn't.

These are all presumptions, but if we had information that maybe is additional information in

pointing to the drug's efficacy from what we come up with as a Written Request include, you know, whether or not there is dosing information or pharmacokinetic information that helps to point, almost like dose-response kind of information, so if we had that and then requested in addition the 3891 as sort of an additional piece of information that, you know, at the end of the day may mean that all of that together, maybe 3891 in and of itself wouldn't be sufficient but that plus some of the additional information that is going to be part of this new Written Request that we develop, does the committee think that there would still be some utility in trying to sort of put all of that together? Dr. Finkelstein said, you know, to look at all the experience with this drug. So, sort of doing sort of a global-Basking the very specific focused questions that we can regarding optimizing dosing, which includes formulations and PK and maybe PG etc., but then also having sort of an umbrella submission of existing data and the level of detail of that additional data could vary. You

know, it could be lots and lots of primary data. It could be certain types of primary data with the rest of it being literature etc. To all come together as a package that might sort of mutually support each other. Did I ramble on enough with that question?

DR. LINK: I worry about the fact that you are going to get into a cooperative group trial that is ten years old and you are going to find that patients are lost to follow-up, that you have all the problems of the things that you wish you had that you didn't collect prospectively and/or the incompleteness of data and you are going to be trolling back at the institutions. I know we are not supposed to talk about cost but that is where all the money is going to go instead of for the things that we are really interested in, which is item number two. That would be my fear about trying to entangle them again.

DR. WEISS: So, I guess the thing then is could there still be some utility in focusing our efforts in a Written Request on the issues for item

to, not losing sight of the fact that there are data, published literature, additional information that might help bolster whatever data we come up with and get as part of question two? I mean, again, for the dose-response kinds of information, if you can really have some solid information that looking at, you know, both efficacy and toxicity and dosing information, you know, that can be very solid data. Maybe if you have all that you don't need the other information. I guess I am trying to think, you know, is there a potential way at the end of the day to still have the information that potentially could be suitable for an indication.

DR. SANTANA: Let me follow-up on that, Karen. Do you envision that potentially the Written Request could ask and review a body of studies that demonstrate the activity-- on purpose I did not use the word efficacy--the activity of this agent in neuroblastoma that then the label, without giving an indication, specifically demonstrating safety and efficacy could provide some information about the potential activity of

this drug? So, you really wouldn't go for a supplemental NDA in the sense of safety and efficacy data but you would request information that would really help us settle the field in terms of what is the real activity of this drug.

DR. WEISS: Yes, that is--

DR. SANTANA: I know it will become an internal issue--

DR. WEISS: Right.

DR. SANTANA: -Bwhen you guys look at it. Maybe that is a way of getting that body of data and having somebody review it independently and give us some indication about the role of this drug.

DR. WEISS: I mean, that is certainly an option. I mean, I think we all agree that it is important to get further information, important information on how best to use the drug. If that information, in addition to maybe some additional data from published studies, whatever, is strong enough in itself--we would have to decide where that information is best appropriate for the label.

Whether or not it rises to the level where it could be an indication; whether or not it doesn't have a specific indication but still provides information, I think those are all potential options that we would have to look at, at the end of the day and we probably can't make any kind of a priori decisions on how that would play out.

DR. RICHARDSON: Can I ask a question? Is it the feeling among pediatric oncologists that the activity of this drug is a closed issue? I mean, this is pretty well settled?

MR. HUTCHISON: I am not a pediatric oncologist but when my son relapsed they did a consult with the guys at Sloan-Kettering and their official thing to me wasB-and it is kind of an interesting question, but they said they don't believe in the activity of it, but what they believe is it is not toxic and so they were answering a different question. That is what they said. So, I just wanted to throw that out there.

DR. LINK: Safety and efficacy is what we are looking for. But I think that this was

presented at a plenary session of ASCO, the abstract, and the publication was in the New England Journal of Medicine, peer reviewed. And, we have seen the updated data. You have to say do you believe the data or don't you.

DR. MORTIMER: I don't mean to insult my pediatric colleagues here, but, you know, because you don't have a huge denominator for any of these studies I think the most amazing thing is that the study got done with a large number of patients. But I think if that was an adult study we wouldn't consider that a positive study.

DR. LINK: Those are years at the bottom.

DR. MORTIMER: No, no, no. I understand they are years at the bottom. We have lived through using Iressa that was a loser at the end. I mean, history would dictate that the first blush is not always correct.

DR. SMITH: I think there are a couple of points. One is it is very uncommon in pediatric oncology to have two trials on the same question on therapy, probably with ALL, which is the most

common and we have repeated studies. Here there is the European data that is different from this but there is an explanation for that. I think when you look at the data for the factorial design and there appears to be a well-behaved factorial design, the test of proportions appears to be robust both for the event-free survival and the overall survival. I mean, these are data that provide reasonably good evidence for effectiveness with this, and I think witness the COG studies and neuroblastoma community in general, it has been accepted as reasonably good evidence that this is an important treatment to continue after bone marrow transplant.

DR. RICHARDSON: If I remember right, factorial design also is supposed to incorporate the lack of an interaction between the two arms. And, you can look at this last slide again and say, well, there has to be an interaction between cis-retinoic acid and the transplant and if you say there is that interaction the other three arms look alike.

DR. SMITH: Yes, I was focusing more on the

event-free survival slide on page ten, which was the primary endpoint. So, I think overall survival is an important metric but the primary endpoint of the study was event-free survival. There, the event-free survival layers as you would expect based on the contribution of transplant and based on a more or less additive contribution of 13-cis-retinoic acid, so without interaction. So, the study did have an interaction monitoring built into it and for the primary endpoint, you know, there wasn't an interaction.

DR. RICHARDSON: But looking at the event-free survival, and I can't see this top line very well, but obviously the two transplant arms pretty much overlap, and could one not say that perhaps a study that really is begging to be done, rather than some sort of 2 X 2 randomized, would be just some sort of two-arm study, if one could accrue the patients quickly enough to satisfy people, to just look at that issue of transplant plus or minus retinoic acid?

DR. SMITH: Well, we do have data from the

current trial, the most recent trial, where it shows that the outcome for patients who got-Beverybody got transplant and everybody got cis-retinoic acid and that curve is superimposable on the best curve of this trial. In other words, this is not going to show regression to the mean, that that was an outlier positive result. That is actually recapitulated in the current trial, and it is not randomized. But you have a confirmatory thing. So, unless you say that all the other arms were by chance losers, you know, the winner or the aggregate arm of the current study is sort of superimposed on the best arm of the study that Kate presented. So, I mean, there is some confirmatory evidence in play. It is not published yet but it is available.

DR. PAZDUR: Could I bring some closure to this? Perhaps what I could suggest is, before we request anything as far as bringing in data because this requires a lot of time and effort, that the FDA staff and NCI staff and COG staff meet together to discuss what shape this data is in, number one.

What are the results of the study, the top line results of the study and review these more internally before we request anything, because what I can see here is that there are a lot of questions here. What were the prespecified endpoints of the study; what was the statistical analysis plan; what was the management of alpha allocation, all of this has to be looked at quite carefully. One has to ask what is the benefit of getting this approved and what would be the ramifications on the pediatric oncology community, and reimbursement if this got a non-approval. That is a double edge of a sword here. So, before we do anything and put anybody into any predicament, I think we should probably have greater internal discussions on this whole issue with the principles of the studies.

DR. LINK: You don't get to vote.

DR. WEISS: No, but it also sounds like we have some important work to do in terms of a Written Request that will encompass some of this additional information and then, as Dr. Pazdur so well described, to put on the sort of back burner

the issue of the randomized data and other existing completed data until we have some additional internal discussions and discussions with the external experts on that.

DR. LINK: Okay. So, no further comments or business? We stand adjourned.

DR. WEISS: So, I would like to thank everybody for their input. Does somebody have a comment? No? I would like to thank everybody. I am sorry, Loice, did you want to comment?

DR. SWISHER: I just wanted to say that cis-retinoic acid is looked at in other communities besides neuroblastoma. You look at medulloblastoma and even some of the glioblastoma, using it after the end of treatment, sort of like neuroblastoma. So, the decision from here on what is going to happen with neuroblastoma is going to affect other childhood cancer because you are further ahead with neuroblastoma.

And, on the issue about funding, perhaps Accutane is not as expensive compared to other things but even if it is $50, $60 a month, if they

lose one parent who can't work, that is a lot of money to a lot of families. So, having that indicationB-some prescription plans are wonderful but there are others that aren't and it could be a problem and delay their ability to get that even if you can petition the drug company about it.

Finally, this may not be that expensive and everybody knows it here at the table, but is this going to be sort of a sentinel event to be precedent where, if you were looking for maybe a avastin for an adenoma [?] you are looking at spending $9,000 a month, you might need that FDA approval to be able to get that funded.

DR. PAZDUR: Here, again, I want to emphasize to everyone here that our decision should be made on the basis of substantial evidence results of clinical trials. The FDA does not make regulatory decisions based on finances, on financial considerations. I just want to make that explicitly clear for the record. End of discussion.

DR. WEISS: I want to thank everybody for a

really informative and very interactive meeting. Both sessions have been very interesting and I very much appreciate everybody's input and expertise.

DR. FINKELSTEIN: Michael, one other thing. There are two people that Karen didn't acknowledge that have put up with a lot of us, and that is Mimi and Charlene to try and get us here. I know they had a lot of challenges right across the board so I think we should acknowledge Mimi and Charlene for getting us here, and we appreciate it. Not only that, they are in charge of getting us to the airports. So, please thank then.

[Applause]

DR. SANTANA: And I want to say some final words based on what I have done this past year, and I want to thank Rick, and Karen, and Ramzi, and Justina, and Lisa, and everybody at the FDA who has been very supportive of my stay here. I think those in academics should seriously consider using my example. It is something that potentially they could benefit from in the future because I think the agency would benefit from partnerships with

academics. Thank you so much.

DR. PAZDUR: And just to conclude that, thank you, Victor, for providing much of the insights, and a delightful friend of the FDA. Thanks.

DR. LINK: And a great presentation this morning. We stand adjourned.

[Whereupon, at 3:40 p.m., the proceedings of session II were adjourned.]

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