wouldn't impact.

What would impact and did impact in various parts of the world was the introduction of CT, an increasingly high-resolution CT scanning during that period of time.

That was as much true in the U.K. as it was in the U.S., and of course leads to the earlier diagnosis of disease-free survival -- the early diagnosis of relapse and therefore identifying when patients become sensitive to disease-free survival.

I think that that is one of the reasons why I have been so convinced by what I've seen so far. Because the surrogate market, disease-free survival, can change with your assessment of what is disease-free, and that is technology dependent and technology driven. The one thing that doesn't change and isn't technology driven is whether you are alive or dead and whether you survive or don't.

Thank you.

DR. MORTIMER: Okay. My second question is either to the Sponsor or to FDA reflected toxicity. I think the FDA said that there was no difference in the

four arms around electrolyte imbalance.

I just wondered if as a signal of activity of this agent there is a higher incidence of ototoxicity, and was that true across both arms, both experimental arms, that they were the same, or is there a difference in the B arm with the addition of MTP?

DR. DINNDORF: I think Dr. Meyers addressed that in his initial presentation, that there is a difference in the -- or maybe it was Dr. Kleinerman, there was a difference.

(PowerPoint presentation is in progress.)

DR. MEYERS: I think that in my opinion this is clearly, the ototoxicity observed in this trial was clearly the result of cisplatin. Because of the protocol design, remember patients in -- it's actually the next slide -- Regimen B did not receive cisplatin during induction.

Patients in Regimen B received all of their cisplatin during maintenance. Patients in Regimen A received two of their doses of cisplatin during induction and two during maintenance.

The opportunity for an interaction between

cisplatin and MTP was clearly more marked in Regimen B, but the excess of ototoxicity was observed in Regimen A-plus, which leads me to believe that what we are seeing is a random fluctuation.

DR. DINNDORF: I mean, I think that it most likely appears to be a random fluctuation as well from my evaluation.

CHAIRPERSON HUSSAIN: Dr. Adamson.

DR. ADAMSON: I'm trying to get a handle on what are obviously very disparate conclusions on what I would say are essentially the same set of data. I fully understand and appreciate the analysis that the FDA has done in trying to drill down on this data.

The question I will pose first to Dr. Blumenstein and then to Dr. Lu. A 2005 publication came out that said there was an interaction using disease-free survival as a primary endpoint. I think the fundamental differences rest upon is there an interaction, or isn't there an interaction? I don't think I understand what the right answer is.

My question to Dr. Blumenstein, was the 2005 published analysis correct? What has changed since

2005, or do we still have an interaction at the disease-free level or do we not have an interaction at the disease-free level? And that's okay.

Then, the question is to the FDA, do we have an interaction at the overall survival level, yes or no?

The questions, again, disease-free interaction analysis in 2005 that was published, is it correct? Does the disease-free interaction still exist?

Then, to the FDA, is there an interaction at the overall survival level? DR. D'AGOSTINO: I just want to jump in here. I did ask that question. I asked the question about the interaction, because I had the same question you do. I'm glad you circled back to it.

DR. MILLS: Thank you. I think it's important to start by pointing out that the 2005 publication is not the same dataset as used for the NDA submission. In that publication, patients with unresectable disease declared at study entry were included, and only patients with metastatic disease were excluded from that analysis. In addition the

endpoint used in that analysis was event-free survival rather than the disease-free survival endpoint that is specified in the protocol. I would like to ask Dr. Blumenstein maybe to comment further on your question about the quantitative versus qualitative interaction.

DR. BLUMENTHAL: There is an interaction in the 2003 intent to treat analysis, and that was indicated in the slide that I showed which shows that the test for the interaction term's P value is .06, but this interaction is quantitative not qualitative.

I think that our interpretation of the data is that this quantitative interaction does not interfere with the interpretation of the marginal test of the MTP effect.

The FDA's approach was to analyze the study as four arms where they regarded the A-minus arm as being the control arm and then proceeded from there.

With respect to the survival, there is no interaction in survival. We have done that test and that's true for both the 2003 and the 2006 datasets.

DR. ADAMSON: Can you clarify for me in the 2005 publication, and I understand the difference between "event-free" and "disease-free," it very clearly stated that if there is an interaction, you can't pool the analysis? Is that correct or no?

DR. BLUMENSTEIN: Well, if there is a qualitative interaction, then it becomes very difficult to pool across the other factor because the interpretation is that the MTP effect is in the opposite direction depending on which chemotherapy arm is being looked at.

If there is a quantitative interaction, then you can pool as long as you understand what you are looking at is the average effect across the chemotherapy arms.

Now, I would like Dr. Meyers to present the 2005 publication. I wasn't involved in that.

CHAIRPERSON HUSSAIN: Dr. Meyers, if you don't mind, be very brief because we have a lot of questions.

DR. MEYERS: Well, the answer is I don't know whether we had a quantitative or a qualitative interaction. We made that conclusion, but our feelings

about the data and the analyses have changed dramatically based on the increased followup data available and the re-analysis.

I will just tell you that in the COG analysis, which is an EFS-based analysis on a different group of patients, there is no interaction by conventional testing, qualitative or quantitative, for EFS in the 2006 dataset.

CHAIRPERSON HUSSAIN: Dr. Lu, do you want to respond to the same question?

DR. LU: For overall survival, we don't observe obvious treatment by regimen interaction, but in DFS we do. Even putting aside the overall survival, even when say there is no obvious treatment by regimen interaction for overall survival, as we stated, the inadequate followup for overall survival made it impossible to perform any meaningful analysis.

CHAIRPERSON HUSSAIN: Can you please clarify for those of us who are not statistically wise, the comments that Dr. Blumenstein made about "quantitative" and "qualitative," do you agree with that statement, that there is a qualitative; correct?

What did he say?

DR. BLUMENSTEIN: (No microphone) Quantitative.

CHAIRPERSON HUSSAIN: Quantitative. That there is a quantitative not a qualitative, and therefore it is okay to pool.

DR. LU: I don't totally agree with that because basically there is one for A-plus versus A. There is no effect in that comparison for MTP, so no effect versus effect to me it is a qualitative interaction.

CHAIRPERSON HUSSAIN: Dr. Helman.

DR. HELMAN: I have two questions actually. The first question is pretty trivial. I'm curious why a chondroblastic osteosarcoma was excluded from your dataset. I don't' understand that at all.

My second question is to IDM. Given I gather that the study closed for accrual in November 1997 and it was published in March 2005, I gather somewhere between the last ten years there have been discussions between IDM and the FDA.

I was curious if there was ever any

discussions to at least clarify some of these issues with additional clinical studies, or if there are any additional clinical studies that are currently proposed?

Go to the FDA to answer the first one.

DR. DINNDORF: Based on my reading of the inclusion and exclusion criteria listed in the protocol, it seemed to be excluded. It doesn't make a difference in the overall analysis whether you included this.

DR. MILLS: IDM didn't acquire the Jenner assets until 2003, which is the first time we had access to the data or any information about this product.

At that time the product was no longer available for investigational use. We had to reinitiate all of the manufacturing, the contract manufacturers, and produce several lots of product and demonstrate comparability, so it was not until last year that we had actually had product available for investigational use.

We did initiate a study recently in patients with metastatic disease. There are to date no patients enrolled on that study. It is open currently at a single site, but there are plans to expand it probably

after we modify it. About a dozen patients have been screened for that study, and so far none have been eligible, so all eleven have been treated under compassionate use.

CHAIRPERSON HUSSAIN: Is this a randomized trial, or a single arm?

DR. MILLS: It is a small randomized trial on patients with relapse disease.

CHAIRPERSON HUSSAIN: Thank you.

Dr. Perry.

DR. PERRY: I have a comment and then a question for the Sponsor. In the 2005 article, I quote: "We consider that Regimen A-minus -- cisplatin, doxorubicin, high-dose methotrexate -- without MTP the standard arm of the trial."

As far as I was concerned, that regimen was the standard arm. Why then did MTP not add any benefit to the standard arm of the trial?

DR. MILLS: Well, I think it is important to remember that the study was not powered to look at the individual arms, but I would like to ask Dr. Meyers to comment on that.

DR. MEYERS: I think what I would like, first of all, is to get forgiveness for having said that in the paper, because I don't believe that it's true.

(General laughter.)

DR. MEYERS: It's my paper.

DR. PERRY: Yes. I'm quoting you.

DR. MEYERS: I'm disavowing it. The second answer is, first of all, the study was never powered to look at differences between arms. It was powered for the factorial analysis.

Secondly, I think that the appropriate comparison is, in fact, the pooled analysis comparison which shows the difference.

Thirdly, I think we have mentioned that there are significant ascertainment issues which may have resulted in differences in the timing at which recurrence was detected, and those issues are completely obviated in the overall survival analysis which shows a clear benefit for both arms with no sign of interaction.

The final point that I would make is that there does appear by chance to be a randomly increased frequency of inferior necrosis in Regimen A-plus, that

is, the patients who were randomized to received chemotherapy with three drugs and then to receive MTP in maintenance.

By chance, there was a higher proportion of those patients who had inferior necrosis at the time they entered maintenance, which may explain the reason that we did not detect the enhanced DFS in Regimen A-plus.

DR. PERRY: Well, if I understood you correctly in your answer to Dr. Hussain earlier, you considered this three drugs to be the standard of therapy for 2007.

If this drug were approved, I would then assume that you would be adding MTP to the three drug regimen that you just discussed. I would find it hard then to believe that you would have any confidence in adding the drug to something that had been proven by your own study to be inferior.

DR. MEYERS: I'm not sure that I can understand your characterization that we proved something to be inferior.

DR. PERRY: Well, A-minus MTP didn't add

anything to Regimen A.

DR. MEYERS: Again, the study was not powered for that. You are looking at DFS data in isolation without taking into account the overall survival data which obviates the question of ascertainment bias. On balance, there was a benefit for both of them.

If this failure to detect signal in A-plus was due to a random excess of inferior necrosis in Regimen A-plus, then it's very likely that there was benefit with both chemotherapy regimens.

Again, I must take issue with the characterization of three-drug chemotherapy as standard of care. We have not established a standard of care for this disease. We are in the process constantly of trying to do so.

CHAIRPERSON HUSSAIN: Dr. Reaman.

DR. REAMAN: Dr. Reaman, I have a couple of questions. I guess, first, if the study wasn't powered sufficiently to address the issue that was being questioned, I don't think it was powered also to address the issue of overall survival. How have you overcome that difficulty?

DR. MILLS: I would like to ask Dr. Blumenstein to comment on that.

DR. BLUMENSTEIN: Well, we don't regard overall survival as a secondary endpoint. We regard overall survival in the same that one would if you were under the accelerated approval paradigm, that is, disease-free survival is a putative surrogate for overall survival.

We wouldn't be here if we didn't really have both endpoints positive. Under those circumstances, there is no need to share alpha between them. There have been some comments made about the lack of precision in the specification of the survival analysis in the protocol.

It's true that survival analysis wasn't described, the method wasn't described, the timing wasn't described and so forth. On the other hand, the survival analysis was done the first time when we received the 2003 dataset.

Mark Krailo confirms that there were no previous survival analyses done because a number of events were insufficient prior to that. What we are

featuring here is the 2003 survival analysis as an analysis of the reference endpoint for the putative surrogate endpoint of disease-free survival.

DR. REAMAN: I want to ask my second question, then, because I think you've addressed it. You didn't think there was an erosion in the alpha.

The other question is for the Sponsor, and that relates to the dose, the recommended dose of MTP should it be approved. Given that there was an escalation in the trial or a proposed escalation, it's not clear to me if it's going to be 2 milligrams, 2 milligrams plus 1, 2 milligrams plus 2.

Is there any information that the Sponsor can provide as to what the recommended dose of this agent would be and in combination with what chemotherapy?

DR. MILLS: In answer to the first question, I think it is important to note that only 28 patients in the ITT group actually had those escalations. Very few patients actually had those escalations, indicating that most patients do demonstrate one of the biological effects at the 2 milligrams per meter square dose.

Currently, in the submission, the Sponsor has

recommended dosing to be according to the dosing in the Phase III study, that is, a dose-escalation schema based on demonstration of biological effects as described in that protocol.

Your second question?

DR. REAMAN: With what chemotherapy?

DR. MILLS: With combination chemotherapy.

DR. REAMAN: With combination?

DR. MILLS: We have not specified, and we are specifying with multiagent chemotherapy.

CHAIRPERSON HUSSAIN: Can I ask you question, please? Because I don't treat sarcomas, but I look at the curves there and it seems to me the three drugs do better than the ifosfamide side. The ifosfamide side without MTP seems to cause worse survival.

How can one put on a package insert whatever three-drug choice the doctor has when you can see that there is a huge difference between the outcomes?

DR. MILLS: Well, I disagree that there is a huge difference between the outcomes. Again, most of these differences are not significant, and the study was not powered for this endpoint. I think which drugs that

would be used in the labeling would be in negotiation with the FDA when we got to that step.

CHAIRPERSON HUSSAIN: Dr. Mills, I would like to just for the record take issue with that comment, because I cannot believe that if you were the advising physician for patients in the clinic that you would look at the ifosfamide arm and say that that ifosfamide arm without the MTP is actually an acceptable arm.

DR. MILLS: Well, I'm not a treating physician, so I would like to ask Dr. Kleinerman to comment on that, please.

DR. KLEINERMAN: Okay. Let me just emphasize that there really is not a standard of care for treatment of osteosarcoma. For example, in our adult physicians at MD Anderson do use ifosfamide up front, so they would use a four-drug regimen.

I would recommend using MTP with either three drugs or four drugs based on the overall survival. Because it doesn't matter whether you use three drugs or four drugs, your overall survival is going to reach approximately 80 percent, which in the end is what you want to see.

You want to have a live patient at the end of eight years or ten years, so I don't think it really matters clinically whether you use three drugs or four drugs.

Also, the way you give the drugs and the time you give the drugs is physician-dependent as well. I don't think we know the best way to give MTP with combination chemotherapy, and I think more investigation is needed to decide what the best timing is. But if we don't have the drug, we can't study it.

CHAIRPERSON HUSSAIN: Dr. Harrington.

DR. HARRINGTON: Thank you. This is clearly a study which seems quite sensitive to how it is analyzed and so it opens up lots of questions about the background data, three datasets versus one dataset, interaction versus pooling. For me I think some of it hinges on the quality of the background data. There are three questions that I have there either for Dr. Krailo or for the FDA or for the Sponsor, whoever can answer it best.

There were 46 versus 14 removals from the MTP arm versus the non-MTP arms pooled for patient

preference. I would like to know if anybody has the data on what happened with those patients, not why they were removed, but happened subsequent to removal? Because, in fact, they might have a very large effect on the analysis.

The second question is, Dr. Krailo explained the asynchronous nature of case report forms and electronic datasets. Presumably, with an asynchronous data flow, there are other case report forms or modifications to case report forms which provide validation for what is going on in the electronic dataset even those are coming in from other studies. I would like some comment on whether there is paper documentation for those differences.

Then, the third is the followup for survival. It has been raised already that there are a very large number of people, once children now adults, treated on this study for whom survival is not available, some going back more than seven years or so.

I would like to know about the efforts that have been made to try to update that survival and whether or not there are possibilities for selection

biases by arm in that.

DR. MILLS: Okay. I will take them, the ones I can address first, and then I will ask Dr. Krailo to come up and address his.

The 46 patients that were discontinued from therapy for voluntary withdrawal were described. I don't have a separate outcome of those. I can get that for you, if you would like to see it, later.

However, it is important to note that those patients who withdraw from therapy continue to be followed by the COG for events, so those patients would not be excluded from the pool of patients being followed for events, and I think that is very important to note.

Secondly, the followup for survival in the 2006 dataset is, first of all, the same between study arms so that there is no selection in followup as was shown in the slide that Dr. Meyers showed. We will get it up here for you in a minute.

Secondly, looking at the numbers, we have focused in the survival followup on the first five years because this is the time when patients are most at risk for an event.

In the 2006 dataset, 95 percent of patients are accounted for. Here is the comparability of followup shown here.

(PowerPoint presentation is in progress.)

DR. MILLS: In the 2006 dataset, 95 percent of patients are accounted for at 3 years and more than 80 percent at 5 years. COG made an effort, as you heard in 2006, to collect additional followup for the Sponsor.

We are continuing to focus on the fewer than 20 percent of patients for whom there is less than 5 years still in the 2006 dataset, and efforts are ongoing by the Sponsor.

We are now in direct contact with those sites where those patients were from to try to gain the additional followup for those. I think it's about 18 percent.

DR. HARRINGTON: I will ask a followup question to that then. Is there any evidence or intuition about the possibility of late side-effects from MTP that may not be picked up with the lack of long-term followup on these kids?

DR. MILLS: Well, I think there is fairly

long-term followup. I would like to ask Dr. Kleinerman. There is no evidence of any long-term effects. She certainly knows more about it than I do

DR. KLEINERMAN: Okay, so the Phase I study was initiated in 1986, and then I did a subsequent Phase II study. There are patients that we have 10 and 12 years out, and we have no seen no late effects.

As far as we know from the patients that I followed in my Phase II study, we can't see any late effects in terms of second malignancies, hearing loss -- not hearing loss, mental defects, any of the typical things that we follow in pediatric oncology.

DR. MILLS: Maybe Dr. Krailo can comment on your question about data.

DR. KRAILO: I'll talk about the issues, two issues, that I think that are relevant here. One is a CRF that would appear in a chart that don't appear to be represented in a database, those are data that don't pass quality checks.

Also, the CRFs that would come to be reviewed would be reviewed by a data technician who if she identified what looked like an unreported event, this

case would go on a query list that we would actively followup to insure that the institution has submitted all its requisite data for that study.

In a few cases, there was followup that was taken from other datasets, if the patient had recurred and then gone on to another COG study that required followup so that their followup was submitted on case report forms for that second study.

We would use the quality checks for those data to update survival data, and we would then fill in our electronic dataset with those followup data after they passed the quality checks for the overall patient history within their first study and within their second study.

DR. HARRINGTON: Were those second case report forms not made available to the FDA in their review of case report forms for survival data?

DR. KRAILO: They are not part of our patient charts for those records, that is true.

DR. HARRINGTON: When there is a query process, does that not get documented in the patient charts?

DR. KRAILO: It does not get documented in the CRF chart we have. We keep a separate data manager log book. Most of it had to deal with the database system we were using and how it presented records aggregate, aggregate reports across patient. It was just much less paper, much less filing to keep the log book of open queries separate from the individual patient charts.

DR. HARRINGTON: Did the FDA ask for these additional records and see them?

DR. KEEGAN: The FDA asked for updated datasets in February or late January or February, and we received a dataset with no supporting documentation in April. We have not had an opportunity to discuss this further.

CHAIRPERSON HUSSAIN: Can I just ask the same question here? Is there a plan to get those records and then for you to review them?

DR. KEEGAN: For the 2006 dataset, we have not made a firm plan as to whether or not we are going to request additional information. I think we wanted to hear the comments of the Committee first.

CHAIRPERSON HUSSAIN: I take it that means

that in your opinion the forms will not change your assessment, whatever you presented?

DR. KEEGAN: It won't change our assessment of disease-free survival, which was the primary study endpoint.

CHAIRPERSON HUSSAIN: Dr. Adamson.

DR. ADAMSON: Well, I want to come back to the overall survival because I think we have some common ground between the analyses and some outstanding issues. You have 80 percent followup at 5 years.

Dr. Dinndorf, you mentioned that there were 26 patients who we can predict probably would impact on survival.

Am I to understand that those events, therefore, are not in the analysis? But if they were, since I think it was 16 versus 10, how would that impact the overall survival results? Has that kind of analysis been done? Or, maybe Dr. Lu can answer that.

DR. DINNDORF: We haven't done that sensitivity analysis.

DR. MILLS: We have done that. We have done that sensitivity analysis. First of all, I want to

clarify. Actually, of those 26 patients, 11 were in the no-MTP group not 10; so, it was a slightly different number.

In the 2006 followup data, 12 of those patients have several additional years of followup, six in each, no-MTP and MTP arms. In the MTP arm, those six patients all are deaths, and those are all recorded as deaths in the 2006 dataset.

In the no-MTP arm, four of the six patients with several additional years of followup were still alive at the last contact, so it is probably not appropriate to assume that they all died.

We also did the sensitivity analysis assuming that those who were not accounted for in the 2006 dataset were considered dead. Dr. Bekele can tell you the results fo that.

(PowerPoint presentation is in progress.)

DR. BEKELE: We did a very straightforward sensitivity analysis. We took the patients who were assumed to have evidence of disease and assumed that they died on the date of last contact, and then performed a stratified log-rank test as the per-

protocol methodology.

Our P value was .046 for the 2003 ITT dataset with a hazard ratio of .75, so it didn't affect the overall estimate. The 95 percent confidence interval for the hazard ratio was .55 to 1.01.

Now, when we did the same thing for the 2006 dataset, the P value was .04 with a hazard ratio of .55 to .98. Now, the reason why there is less effect in the 2006 dataset as opposed to the 2003 dataset is because there were more events.

Some of those patients who had a vast evidence of disease had events and so there is less of a change, when you change the ones that didn't change, to having an event.

CHAIRPERSON HUSSAIN: Dr. D'Agostino.

DR. D'AGOSTINO: Some of the questions I wanted to raise have been addressed, but I do have a couple more questions.

On Slide 13 of Laura Lu's presentation, there are the four separate groups. This discussion, this is the disease-free survival, there is this discussion about the quantitative versus qualitative.

If you look at that graph, the differences between including the new treatment versus not are really driven by the B Group. I just would like the Sponsor to say one more time what are they talking about in terms of qualitative and quantitative when you look at that curve. This is Slide 13 of Dr. Lu's talk.

DR. KEEGAN: The statistics?

DR. D'AGOSTINO: The statistics, yes.

(PowerPoint presentation is in progress.)

DR. D'AGOSTINO: What makes the pooled analysis work is that you are pooling the upper two curves with the lower two curves. I guess you could say in terms of MTP that may be quantitative. But in terms of B it is, why not qualitative? I mean, B is what happens, how you group B drives the analysis quite a bit.

DR. MILLS: Dr. Blumenstein has actually also done tests for qualitative interaction on the chemotherapy as well as the MTP effect.

Dr. Blumenstein, would you like to comment on that?

DR. D'AGOSTINO: I mean, do you defy the data

that is sitting there?

DR. BLUMENSTEIN: Whether something is labeled as a qualitative or quantitative interaction depends on identifying one of the factors as what you are interested in and the other factor as being secondary to that.

DR. D'AGOSTINO: Well, that's what I'm saying. If you go to the MTP, you get that. If you go to the B, you don't get that.

DR. BLUMENSTEIN: If you go to looking at whether the interaction with respect to chemotherapy is quantitative or qualitative, it appears to be qualitative.

However, we did a statistical test, the maximum likelihood test, the Gail Simon test, and we failed to find evidence of a qualitative interaction even for the chemotherapy regimen.

Now, what that is really saying is that we have very low sensitivity I think to be able to detect these things. But I keep coming back to the idea that what we're talking about, the only time we're talking about interaction, is in the context of disease-free

survival, and these things just aren't present for survival.

DR. D'AGOSTINO: Well, it's just very hard to say A versus A-plus MTP. The other question I have is I'm just a simple statistician from Boston, and I just don't have the faintest idea of the followup on the overall survival.

The FDA is saying that more than 50 percent of the 530 patients alive at the last contact were lost to followup, and now I'm hearing that there is 80 percent followup for 5 years. Is the FDA wrong? Are they using old data or--?

DR. MILLS: The followup that I quoted 80 percent are accounted for at 5 years is based on the 2006 COG dataset.

DR. D'AGOSTINO: I mean, did you sensor? I mean, because I think part of the FDA problem is that you were sensoring observations or subjects when they sort of dropped out of the study. When you say 80 percent followup at 5 years, you mean you know exactly what happened to those 80 percent, or that they answered the analysis?

DR. MILLS: No, that means we know exactly what happened to those patients at a date beyond five years.

DR. D'AGOSTINO: Thank you.

(PowerPoint presentation is in progress.)

DR. MILLS: Here actually are the numbers for you if you would like to see it from the 2006 dataset for the first five years for the MTP and no-MTP group.

Again, IDM is focusing on attempting to get the additional followup up to five years for any patients for whom we don't know what happened to them at the at least five-year time frame.

DR. D'AGOSTINO: You think the FDA's standard of 5 percent lost to followup is the only tolerable?

DR. MILLS: I would like to get Dr. Meyers to comment on that because of the fact that we are talking about pediatric patients who tend to live sixty or seventy more years.

DR. MEYERS: Well, I'm not sure that that's the reason, but I think that that standard is typically applied in short-term studies of diseases which have a very rapid failure rate.

We're talking about a disease where survival to five years without evidence of recurrence is tantamount to cure. I think in large-scale, cooperative group trials of children and young adults and 80 percent completeness of ascertainment, 5 years or more from diagnosis is excellent.

CHAIRPERSON HUSSAIN: Okay. We have four questions and about three minutes to go, so please make it brief because we are going to break at 10:30.

Dr. George.

DR. GEORGE: To make it brief, just cutting through all of the problems that we have been talking about here, I just want to clarify one particular point, and that is the disease-free survival results by the Sponsor, as summarized on page four of the slides, was that by their approach there was significant results: hazard ratio, .76; P value, .0245.

When the FDA used their dataset and did the same analysis that the Sponsor did, the hazard ratio was .78 with P value of .065. Is that correct? This is Slide 21. I'm assuming that the only difference there had to do with the dataset that was used.

DR. MILLS: I can't comment for FDA, but I don't believe they did the IDM analysis. They did an analysis based on the list of modifications that I described that they made to the 2003 COG dataset. We used the 2003 COG dataset as provided without modification.

DR. GEORGE: Is that correct? I mean, I'm just trying to get -- maybe I should ask the FDA, then. Your slide, Dr. Lu's number 21, your Slide 21 gave a P value of .065. The only difference there is what? It's exactly the same analysis that the Sponsor did but a different dataset; is that correct?

DR. ROTHMAN: Yes, that's correct. I don't need to do so now, but I would like to comment after you're done on the lost to followup on overall survival.

DR. GEORGE: I think I had a further comment about the followup, but that can wait for the open discussion.

DR. ROTHMAN: The analyses that were performed were for DFS and overall survival are time-to-event analysis. You can see from the Kaplan-Meier curves presented by the company for their 2003 overall survival

dataset that there are deaths occurring beyond five years. When you do a time-to-event analysis, it is important that you don't have a lot of lost to followup.

Now, if you're doing a landmark analysis, then it is important that you have followup up to that landmark; or, if you're doing a time-to-event analysis where you have a ceiling for the followup, then it is important to have followup up to that time.

The analysis that is performed by the Sponsor is a time-to-event analysis where it does not have a cap, the ceiling to the followup, and there are deaths that occur beyond five years.

CHAIRPERSON HUSSAIN: Dr. Meyers.

DR. MYERS: I hate to keep reliving this question, but I just have a quick question for Dr. Kleinerman. She basically indicated earlier that there wasn't a difference seen in the ifos-added arm to the MAP arm. Is there current research being done to look for a difference in improved survival?

Because if not, if there is nothing that shows that survival is actually better, why would you consider giving a patient an extra drug without improved survival

with clearly added risk?

DR. KLEINERMAN: Okay. There is no interaction at survival, okay, so four drugs, three drugs. Also, let me point out that the dose of ifosfamide that was used in the ITT trial was 9 milligrams not 9 grams.

There are people who use high-dose ifosfamide. At my institution they use high-dose ifosfamide. They claim that their results, the adult oncologists, they claim that their cure rates or their disease-free survival rates are better. Again, let me reiterate the problem is there is really no standard of care.

Another example at my institution is a lot of physicians give intra-arterial platinum as opposed to intravenous platinum, which can also change things; so, the practice depends on the practitioner.

Dr. Lewis, did you want to--?

CHAIRPERSON HUSSAIN: I'm sorry, I'm going to have to ask you to stop there.

Dr. Blaney, do you have any questions? You've been patient.

DR. BLANEY: My questions have been answered.

Thank you.

CHAIRPERSON HUSSAIN: Okay. I think we are done for this morning. I would like to thank the Sponsors and the FDA and the members for a wonderful discussion.

I'm sorry. What? We're breaking now. I'm sorry. Yes, I would like you to come back in exactly 15 minutes, that would be 10 to 11:00.

(Recess.)

OPEN PUBLIC HEARING

CHAIRPERSON HUSSAIN: We are going to be starting the open public hearing. I would like to read the following statement:

"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, the 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 the Sponsor; its product; and, if known, it's direct competitors.

"For example, this financial information may include the Sponsors payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

"Likewise, the FDA encourages you at the beginning of your statement to advise the Committee if you do not have any 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."

Thank you.

MS. CLIFFORD: Our first speaker is Ms. Nguyen.

MS. NGUYEN: Good morning. My name is Quynh-Tram Nguyen. I live in Exton Pennsylvania and my transportation today was paid by IDM Pharma. I am 28 years old and when I was 12 years old I was diagnosed with osteosarcoma.

I was in seventh grade in Vietnam and during a run I became very tired. I sat down and when I stood up I had a pain above my knee. I thought it was from exhaustion from the running, but the pain did not go away.

For a month, I tried some home treatments, but the pain still did not go away. There came a point when I could not walk normally because of the pain. My mother took me to the hospital. I was diagnosed as having a bone infection, and they prescribed antibiotics.

I took the antibiotics for about three weeks about the pain, but the pain became even more extreme and my leg became swollen above the knee. I returned to the hospital where a physician tried to put a needle into my leg. It was clear there was no infection, so they next did a biopsy.

Finally, after many months of visits, the diagnosis of osteosarcoma was made. This was in September of 1991. The doctor suggested that my leg be amputated right away.

Also, they were not even sure if I can survive

after my leg was amputated. I did not want my leg amputated, so I went home for three weeks to seek alternatives.

A relative living in Australia was able to do some research with a physician who specialized in osteosarcoma. The physician in Australia said that if I were living in Australia they might be able to save my leg. But because it takes a long time to go anywhere, she would advise that my leg be amputated, otherwise my life could be in jeopardy.

I decided to have my leg amputated. The date was October 17, 1991. After that I went home and awaited the medicine from Australia.

The chemotherapy started in January 1992 by Vietnamese doctors following the instructions from the Australian doctor. The medicine was very strong and I had some very bad reactions.

My grandfather was in the military for the former government before 1975, and I was regarded as a political refugee. Luckily, our paperwork came through, and we were able to come to the United States on May 6, 1992.

I was first checked with a specialized doctor in a private clinic, and he referred me to MD Anderson for possible care. At MD Anderson I was introduced to see Dr. Eugenie Kleinerman through Dr. Jaffe (phonetic).

I first visited her in May 1992. She explained that she wanted to place me in a clinical trial for mifamurtide. At this time they found that the cancer had gone into my lung.

I agreed to participate in the trial because there was no better choice for me. I started on mifamurtide along with chemotherapy, and then in August 1992 I had an operation on my lung for cancer removal.

Then, I continued treatment, mifamurtide and chemotherapy, for another three months, until November 1992. After that Dr. Kleinerman told me that I was in remission and was able to discontinue treatment. However, my treatment continued from 1992 -- no, I'm sorry, my checkups continued from 1992 to 2003. I am now a 15-year survivor of cancer.

Today, I live in Exton, Pennsylvania. I am married with two children who are here today with me. I really appreciate the chance that I have to see Dr.

Kleinerman at the right time and to be able to be treated with the right drugs.

I am not a physician and cannot say what contribution mifamurtide made to my recovery, but I believe it helped me. I hope that others may benefit from its use.

Thank you.

(Applause.)

MS. CLIFFORD: Thank you.

Our next speaker is Matthew Alsante.

MR. ALSANTE: Good morning. My name is Matthew Alsante, and I am the executive director of the Sarcoma Foundation of America. Our organization provides funding for sarcoma research and also advocates for public policy that will result in increased attention by government and industry towards the issue of patients with sarcoma and other rare cancers.

The Sponsor today, IDM, has provided modest support of our patient educational program. However, we are here today at our own expense and nothing I am about to say has been cleared by the Sponsor or communicated to them.

In November 2005, this very Advisory Committee met to discuss the issues surrounding drug development for patients with rare cancers. A white paper or report did not emerge from the ODAC.

But when an ODAC member asked on that day about generating a report, the FDA response was that the transcript of November 5, 2005, would serve as the official recommendation of ODAC towards the topic.

Repeatedly and consistently on that day member after member of ODAC concluded and recommended that special consideration and potentially unique datasets would have to suffice if the reality of the clinical development situation was that the usual standards were impossible to apply to a given product for a rare cancer.

For example, on that day after Dr. Gail Eckhardt propose the idea of a "body of data requirement" for rare cancer approvals, Dr. Hussain, today the chairperson of ODAC, commented on page 329 of the transcript, "I agree with Dr. Eckhardt's remarks."

It seems to me it is time to revisit the benchmarks, if there were any benchmarks; and, if there

aren't, perhaps establish some benchmarks. It seems to me the bar has to be set where there is a bare minimum that has to be satisfied.

We applaud the FDA for apparently taking these recommendations to heart in their approval process since that meeting.

For example, in October 2006, an approval by FDA that probably went unnoticed by everyone here but was heralded in our small sarcoma community was the full approval of Gleevec® for a rare sarcoma subtype called dermatofibrosarcoma protuberans or "DFSP."

The data upon which approval was based was as follows: a single 12-patient Phase II study, additional response data from 5 patients from case reports, and a report on a response in a single pediatric patient.

Objective response in these 18 patients to Gleevec was very impressive, but no survival data was available or would ever be available for these patients.

The Sponsor, Novartis, submitted this NDA supplement and issued public statements afterwards, that in light of the rarity, this was as complete a dataset as was or ever will be achievable for this

rare sarcoma subtype.

FDA realized this and therefore gave full approval to this agent for use in this sarcoma subtype based on objective response criteria alone.

We in the sarcoma and rare cancer community understand the limitations on achievable datasets, and, again, are extremely grateful that FDA has allowed Gleevec to get to patients with DFSP sarcoma.

We feel that the indications to be discussed today, osteosarcoma, fully meet the criteria of a rare cancer. To our knowledge, there has never been a targeted drug development program for osteosarcoma before this massive effort you are about to pass judgment on. We commend IDM for their efforts.

Nearly all of the issues today are related in some way to this unavoidable issue of rarity and the extreme complexity of assembling the datatset needed to fly over the usually very high bar set by ODAC.

As in the case of Gleevec for DFSP sarcoma, there is no realistic possibility that such an ambitious survival study that IDM did will ever be able to be repeated.

Another issue today, the IDM product is an immunotherapy, and the issue is post-hoc survival. Therefore, we are very afraid that the public storm over another immunotherapy with the same issue discussed recently at the Advisory Committee for Oncology Products at the Center for Biologics, this is the Dendreon Provenge meeting and its subsequent virulent public turf battle, may make this immunotherapy for osteosarcoma patients being discussed today the pawn in some larger cancer political chess game unfolding.

We hope this is not the case. Children with osteosarcoma and their parents have no interest in getting caught in a political crossfire between various advisory committees or between CDER and CBER. We just want additional treatment options for our children with cancer.

Instead, we hope that as mentioned ODAC members remember their own guidance in 2005 about the realities of rare cancer approvals. With the recent full approval of Gleevec for DFSP sarcoma, based on objective response as a proposed benchmark for the bare minimum of setting the bar, judge the issue today in the

context of the extraordinary rarity and need for osteosarcoma patients.

Thank you.

MS. CLIFFORD: Thank you, Mr. Alsante.

Our next speaker is Kurt Weiss.

DR. WEISS: Dr. Hussain and distinguished members of the committee, good morning and thank you for the opportunity to speak here today. My name is Kurt Richard Weiss. My transportation was provided by IDM Pharma as well as my lodging last night.

I appear before you today uniquely qualified to speak about osteosarcoma and MTP. I am a 1997 graduate of the University of Notre Dame. I matriculated to Jefferson Medical College in Philadelphia in 1998.

During the summer after my first year of medical school, I worked in the laboratory of Dr. Eugine S. Kleinerman in the Department of Cancer Biology at the University of Texas, MD Anderson Cancer Center.

Between the didactic and clinical years of medical school, I spent a year with the National Institutes of Health, Howard Hughes Medical Institute

Research Scholars Program.

During this year, I worked in the laboratory of Dr. Lee Helman in the Pediatric Oncology Branch of the National Cancer Institute. My research involved the investigation of metastatic potential and osteosarcoma and Ewing's sarcoma.

I graduated from Jefferson in 2003 and presently am a fourth-year resident in the Department of Orthopedic Surgery at the University of Pittsburgh. As part of my orthopedic surgery residency, I completed a year of basic science research with Dr. Johnny Huard during which I investigated the roles of growth factors in osteosarcoma metastases. This research has been published in "Clinical Orthopedics" and related research.

I recently received a grant from the Orthopedic Research and Education Foundation and Depuy Orthopedics to continue this osteosarcoma research. In two years, I will begin fellowship training in musculoskeletal oncology at the University of Toronto.

However, I'm not here today in my capacity as an orthopedic surgeon or an osteosarcoma basic

scientist. I am here to tell you about my own personal experiences as an osteosarcoma survivor who participated in the clinical trial for MTP.

In the spring of 1989, I was a 15-year-old freshman in high school. I was involved in many activities including the football and swim teams. I attributed the dull, aching pain in my right tibia to a muscle sprain.

In order to humor my mother, I reluctantly went to a sports medicine doctor who was horrified by what he saw on X-ray. That was Wednesday, 10 May 1989, exactly 18 years ago tomorrow.

The next day I was seen by an orthopedic oncologist who took me to the operating room immediately for an open biopsy. We received the diagnosis of osteosarcoma on May 13, 1989. The next day was Mother's Day.

A staging CT scan revealed that I had pulmonary metastases at the time of diagnosis. Prognostically, this was the worse possible news.

As my family and I quickly learned, nobody dies of osteosarcoma in their arm or leg; they die of

metastatic disease to the lungs. In this aspect, osteosarcoma is very predictable. Over 85 percent of metastases are to the lungs, and this accounts for nearly all deaths.

I underwent induction chemotherapy and then had surgery to resect the osteosarcoma from both my leg and my lungs. During my postoperative consolidation therapy with cisplatin and doxorubicin, the cancer recurred in my lungs. It was clear that I had failed the conventional chemotherapy protocol, and my disease was very aggressive.

I will never forget my oncologist's words to us that day, "Mr. and Mrs. Weiss," he said, "from now on we're making this up as we go along."

I headed back for more thoracic surgery to remove the new tumors from my lungs. The plan after that was uncertain, and the uncertainty was terrifying.

My parents were advised to prepare for the worst. Years later, they shared with me that my burial plot had been selected as well as the readings and music for my funeral mass.

At this point we fortunately, I should say

miraculously, heard about Dr. Kleinerman and her experimental osteosarcoma work at MD Anderson. It was a longshot, but it sure beat going home to die. I was willing to try anything at that point.

Dr. Kleinerman determined that I was eligible for her clinical trial with the drug then known as MTP, now known as "mifamurtide."

My mother and I packed our bags for Houston. That was the summer of 1990. I vividly remember that summer in Houston. My mother and I lived at the Ronald McDonald House with families from all over the world. We could not have been more different, but we all spoke the language of desperate hope.

My mother and I spent many hours in the MD Anderson chapel. I prayed for a miracle that the experimental drug would be successful so that I could follow my dream to attend the University of Notre Dame and one day become a physician.

I received mifamurtide for the prescribed six-month protocol, from July through December 1990. My lung scans have been negative ever since. Although I eventually lost my right leg, due to surgical

complications and osteomyelitis, I was given my miracle and survived the battle with osteosarcoma.

Let me now relate a few of the biologic facts that I have learned about osteosarcoma over the years. As we have heard, osteosarcoma is the most common primary tumor of bone, typically affecting patients in the second decade of life.

In the prechemotherapeutic era, when treatment for osteosarcoma consisted of amputation and prayer, five years survival was approximately 10 percent, with virtually all deaths caused by overwhelming pulmonary metastases.

Since the addition of neoadjuvant and adjuvant chemotherapy, that survival percentage has increased to approximately 65 percent for patients without pulmonary disease at the time of diagnosis.

The story is quite different for patients like me who either present with metastatic disease or develop it during the course of our treatment. For us the prognosis is grim.

The infuriating thing for those of us who treat patients with osteosarcoma is that we continually

fail this exact same group of patients, those with pulmonary metastases.

These lung tumors are refractory to both surgery and chemotherapy. That is why MTP is an essential drug. It is the only treatment modality specifically directed toward the prevention and eradication of pulmonary metastatic disease.

To illustrate this point, I offer myself as an example. I left for Houston with micrometastatic disease in my lungs, of this we can be sure because the tumors from my second thoracotomy, which progressed despite simultaneous chemotherapy with powerful agents, showed viable osteosarcoma on pathology.

The natural history of this disease is to recur again and again until the patient's tumor burden becomes too great or the small amount of remaining lung tissue precluded surgery, that is, unless the patient receives an agent specifically designed to combat pulmonary metastases. Thankfully, I am that patient.

I am absolutely convinced, based on everything I know as a physician and scientist, that the only logical explanation for my presence before you today is

that I received a drug specifically targeted toward the eradication of pulmonary metastases.

I stand before you as only one of many patients whose lives have been saved by MTP. While I understand that the testimony of any single patient has limited statistical value, you must understand that as far as my patients, brother, sister, wife, two children, and patients are concerned MTP is 100 percent effective.

Ladies and gentlemen, I don't mean to seem dramatic, but objectively you must agree that my entire personal and professional life has prepared me for this moment, the opportunity to speak with you today. This is absolutely the most important thing I have ever done. I have prayed for an opportunity like this. I appear before you as the representative of far too many friends who should have received this drug but never got the chance.

So many young people and their families have sought me out over the years desperate to receive MTP, but it just was not available. They can no longer speak to you, but I can.

I represent all the young osteosarcoma

patients and their families who are fighting right now to stay alive. Those patients deserve a biologically intelligent drug that combats the deadliest aspects of their disease.

They deserve all the things that I have experienced, everything we wish for our patients: the chance to survive their disease, pursue higher education, chase down their dreams, fall in love, and have beautiful children. Their parents deserve what my parents had, the opportunity to plan a wedding instead of a funeral.

All I can do today is talk, but you have the power to make this happen for them. I implore you as your colleague, please recommend that the FDA look favorably on MTP.

Thank you.

CHAIRPERSON HUSSAIN: Thank you, Dr. Weiss.

On behalf of the Committee, I would like to thank all the public speakers. I also want to assure you that all of us, every one of us sitting at this table takes her or his role very, very seriously. The only single factor that brings us here is concern for

patients, their safety, and their longevity and well-being.

With that, we are going to begin the discussion session within the members of the committee, but there is at least one question that I have here from Dr. Richardson.

Does anybody else have a burning question that they want to ask before we get into the discussions?

(No verbal response.)

CHAIRPERSON HUSSAIN: Okay. Dr. Richardson.

DR. RICHARDSON: I would like to get back to the issue once again on overall survival. I'm just curious whether there are differences among the four arms of this particular study in the numbers of patients who might have undergone resection of pulmonary metastases.

Here, we've got a drug that putatively has some sort of unique action on these pulmonary lesions. I'm curious whether that would affect the aggressiveness with which surgeons would undergo resection and the numbers of pulmonary lesions they might have been willing to take on. Do you have any information on

that?

DR. MILLS: Actually, we did consider that.

Dr. Meyers, I would like to ask you to address that, please.

DR. MEYERS: I think that your question is very well taken, and the answer is we did examine this question. We asked a couple of questions. We first asked whether at the time of recurrence among the patients who had recurrence, was there a difference between patients who did and did not receive MTP and the site of recurrence.

There are large-scale studies that indicate that pulmonary metastases have a higher rate of salvage than metastases at sites other than the lung. We were able to show that there were no between-arm differences in the sites of metastases.

We then asked the question, How many patients were submitted to post-recurrence surgical attempt at curative resection? Once again, there were no differences, there were no between-arm differences in the application of surgery at the time of recurrence.

CHAIRPERSON HUSSAIN: Thank you.

QUESTIONS TO THE ODAC AND ODAC DISCUSSION

CHAIRPERSON HUSSAIN: I'm going to ask that the question be put up there for the beginning.

(PowerPoint presentation is in progress.)

CHAIRPERSON HUSSAIN: Before I ask Dr. Helman to discuss the question, I would like to ask the biostatisticians on the Committee, because it seems to me this fundamentally is a statistical issue here, that if you accept that the data can be pooled, therefore the disease-free survival is acceptable, that means the primary endpoint was acceptable or was met, therefore the secondary endpoints would matter; and, if you don't accept it, then there are a lot of issues that will be caused because of that?

Perhaps, I can ask Dr. D'Agostino, Dr. George, and Dr. Harrington for their opinions, briefly?

DR. D'AGOSTINO: Unfortunately, I think the interaction does exist in the data, that the quantitative and qualitative sort of muddies the water because of selecting what you mean by the treatment that you are pegging in the qualitative. I think so much is driven by what happens to B and B-plus as opposed to A

and A-plus.

CHAIRPERSON HUSSAIN: Dr. George.

DR. GEORGE: Just a general comment about your preface, as I asked an earlier question, there is a discrepancy between the FDA analysis using the Sponsor's approach but based on the data as they had it that refined it. It is right at the edge even in that. I just wanted to point that out.

If you are using the usual criteria, one analysis results in a nominal P value on one side; and the other, on the other. It is still debatable even in that.

As further comment, I personally like factorial designs in general, but they have to be done really well and you have to really think clearly when you are designing them about these kinds of issues. I mean, what is going to happen if you do get interactions? What would your interpretation be?

To me this in some ways is a clash of a scientific kind of analysis as opposed to a regulatory approach, that is, if I were doing this at this point, ignoring the data issues and everything, which are very

important, but just taking the results on face value, I would look at pooled kinds of results but in the following sense.

If you are doing a factorial design, you ordinarily would want to look at the main effects and the interaction. In this case, it looks like it's pretty clear there is a main effect but also an interaction.

That means that you can't interpret the main effects in the usual way, that is, and this relates to what would you approve. Because it would look like if you were writing up the results of the paper, you would say, yes, there was a main effect for the MTP. There is no main effect for the ifosfamide, but there was a pretty big interaction, which means that you can't interpret those main effects in the usual way.

How would you interpret them? You would probably have to say, "Well, as far as we can tell, it seems to work if you're in the ifosfamide group but not in the other group."

What does that mean? You know, that gets very tricky. It is in some ways unfortunate in this setting

that a two-by-two design was used, but of course it wasn't done in a regulatory setting to begin with. It was done in a different era.

These things were obviously not thought through at the time, and I think now they are coming back to cause real problems of interpretation. If, for example, you had said or you had asked yourself, "What would have been the right design for approval?" You would probably have said it should have been standard regimen, whatever that is, versus standard regimen plus MTP.

Now, if you had chosen, it looks like from the results we have, the standard regimen to be the non-ifosfamide group with cisplatin, we wouldn't be here today because the results showed no difference.

The only reason we are here is because of this big difference that has cropped up in the other group, which this is just a difficult matter of interpretation. If you were just writing a paper, you could say, on the one hand, it means this; on the other hand, it means that.

When you are in a regulatory setting, you have

to say, is there sufficient evidence to approve this for wide use in the population? That's I think a difficult problem.

CHAIRPERSON HUSSAIN: Dr. Harrington.

DR. HARRINGTON: Thanks. I think, as Steve said, the interpretation of interactions is always very difficult. In this setting for me, the additional information in the trial make it even more problematic.

If A and B had been empirically approximately equal, and if the effect of adding MTP to both of those had been somewhat different but positive, then I think one can interpret the overall effect of the hazard ratio there as some sort of population average effect because it doesn't really matter what your base regimen is.

In this case, it clearly seems to matter, at least with respect to disease-free survival what the base regimen is. The interaction effect for me becomes much more important there and so I do not favor the pooled analysis here, but, as Steve says, feel that most of the information in this trial is in A versus A-plus.

CHAIRPERSON HUSSAIN: Thank you.

If no one else has a question, I have actually

a question to the pediatricians in the group in terms of, maybe we can begin with Dr. Helman, at least in the context of what was presented, what you view the standards of care are.

Are you bothered by the fact that the ifosfamide arm appeared to be inferior, at least the way we saw it with regard to disease-free survival and so on?

DR. HELMAN: Well, first, let me say that I certainly like Dr. Lewis and like Dr. Meyers and Dr. Kleinerman, we all desperately need better treatment for osteosarcoma. There is no question about that.

I think I agree with Dr. Myers, I would say that the recommendation now is adriamycin, cisplatin, high-dose methotrexate and is considered in the United States the standard of care.

It was like Dr. Weiss commented, we have patients from years ago that recurred that we have cured with ifosfamide, so I have absolutely no doubt that ifosfamide cures some patients. I have no idea how to use it. I have no idea which patients benefit and which patients don't.

I have no understanding of why that arm appeared to perform in an inferior manner. Although, I think, as Dr. Meyers pointed out, it was not statistically designed to ask that question.

There is no question if you compare that curve to what we would consider acceptable outcome, it was below acceptable outcome. That's all I can say really to answer that particular question.

If you want me to make some other comments, or do you want me to wait until other pediatricians have a chance to comment on your question?

CHAIRPERSON HUSSAIN: I was going to ask the other pediatricians to make some comments, and then if no members on the Committee have any questions or comments to make, we can go straight to the question itself and have you discuss it.

Dr. Adamson.

DR. ADAMSON: I can certainly echo Dr. Helman's comments. I have had some sleepless nights since being asked to look at this question because of the desperate needs our patients are facing. The approach in my thinking that I've taken, and I'm still

taking, is to decide what's best for children.

I mean, that's I think at the end of the day what the FDA wants and that's what everyone around the table wants, what's best for children. If we can figure out what's best for children, then we just have to make it work in a regulatory environment.

Now, to paraphrase, the former secretary of defense, you go to the FDA with the dataset you have, not the dataset you wish you had.

(General laughter.)

DR. ADAMSON: This is cooperative group data, and I think if you hold it up against any other cooperative group data, it is excellent. I have no doubt about that. I commend Paul and the company for not letting this go away, for saying "Let's be certain."

The bottom line is it is 2007, and the last patient was enrolled in 1997. If we can't figure this out now, we are not going to figure it out. There are a lot of smart people around the table. The statistical input I think is imperative. I'm learning a lot as we go through the morning. The disconnect, as I see this, is that we

have what is a clear interaction at the event-free survival analysis as published in 2005. I think when I look at the graphs and when I hear the statisticians discuss this, I think there is still a clear interaction at the disease-free survival today.

What raises concern about stopping there is that if I were to sit through a lecture looking at the survival data, it would seem compelling. I mean, the at the end of the day that it what is important.

The real challenge is can we believe it, or is there an underlying problem with how we arrived at the overall survival data. That is I think a struggle for the whole Committee.

I haven't yet made up my mind about how to interpret the overall survival data because it is so difficult. I can say that if this drug was a huge advance, we wouldn't be struggling. We wouldn't be around this table.

Nonetheless, we haven't had an advance in twenty years, and so we can't dismiss what I would say is an incremental advance, if it's there. If there is indeed an interaction at the survival level, we have a

very big problem on our hands. Because I don't think most pediatric oncologists are prepared to expose everyone to ifosfamide in conjunction with MTP, and I don't think the company is asking us to do that, either.

It comes back down to where we are with overall survival and the adequacy of that data. Although I fully agree that five-year followup for event-free survival and I would say 80 percent data is excellent, when you look at the curves and the curves that were shown in Slide 46, there is a lot of activity that starts to spread out those curves after 5 years. We need to be really certain that we have confidence, if we are just going to take a survival analysis, and I haven't yet reached that level of certainty.

CHAIRPERSON HUSSAIN: Thank you. Dr. Reaman, do you want to make any comments?

DR. REAMAN: Well, I would certainly echo my colleagues as far as needing new treatment approaches to this disease and to many diseases in pediatrics, but specifically osteosarcoma. I would also agree with

the statement that it is important that what we do is good for children. I think it is equally important to measure what is good for children by objective evidence.

I think also there is clearly a very strong suggestion, if not objective evidence, of an interaction between the agent being discussed and a conventional chemotherapeutic agent that I don't think is widely accepted as part of the standard of care.

It is not clear to me how this is going to be used, recommended for use. I think where we are now is where we were years ago with the results of Phase I and Phase II studies with some compelling, early clinical evidence of activity of this agent.

But I don't think we have the evidence that we need to say that this should be approved and be part of the standard of care for chemotherapy with nonmetastatic resectable osteosarcoma.

CHAIRPERSON HUSSAIN: Thank you.

Any comments from anyone else from the Committee?

DR. BLANEY: This is Dr. Blaney.

CHAIRPERSON HUSSAIN: Dr. Blaney, go ahead.

DR. BLANEY: I would agree with my colleagues as well. I think that we do want to do what is best for children and that does have to be based on objective evidence.

If we were to incorporate this as a standard therapy without being a hundred percent sure that there was that objective evidence, we could also potentially be exposing many children to the time and inconvenience of receiving treatments, and we aren't a hundred percent sure that it is warranted.

I think the person that has the most experience with this is Dr. Kleinerman, and as she said we don't know the best way to give this with combination chemotherapy and the best timing. If we were to recommend it, we would have those issues to resolve.

CHAIRPERSON HUSSAIN: Thank you, Dr. Blaney.

Dr. Helman, you would like to discuss the question that is posed to us by the FDA, which is on the board there.

DR. HELMAN: Let me just, for those of you who don't know me, I was chief of the Pediatric Oncology

Branch for nine years, and I'm currently the scientific director for clinical research at the National Cancer Institute. I have treated patients with osteosarcoma for over 20 years, and I've studied osteosarcoma in the laboratory for over 20 years.

I think the question really is quite simple. Do the data demonstrate that the addition of MTP to current standard therapy improve the survival in patients with nonmetastatic osteosarcoma?

I think the issues are also quite compelling. One of the issues that I see is there is an issue in the study design about timing of randomization. This was not discussed in detail, but I do not believe this is how this study would be conducted today.

There is the issue of post-hoc analysis of survival; there is the clear issue of potential drug interaction, and the unexpected finding of one arm that contained at least not standard therapy to underperform.

I guess I would actually say that there is actually no doubt that MTP-PE does interact with infosfamide. We have had discussions about this. We have discussed the potential of fast, fast ligand. We

have talked about collaborating with Dr. Kleinerman to try to sort this out. I think it was an unexpected finding.

I think, if I could say, it makes it more imperative that as we do these types of biologically based studies in the future, it is absolutely imperative that we build into it scientific investigations so that we have answers instead of more questions than answers.

I will say to Dr. Kleinerman, I'm sure she was imploring these studies to be done, and for whatever reasons they were not done in the performance of this Phase III study.

I forget who made the comment, but there was a discussion and a comment made that it would be unethical to do a further study. I would make the comment that I believe, given the data we have, it is unethical not to do another study, to do the study that would answer the questions so that we know whether or not we need to give this drug to ever patient who presents with nonmetastatic osteosarcoma. That's all I have to say.

CHAIRPERSON HUSSAIN: Thank you, Dr. Helman.

Dr. Pazdur, just for the record and

clarification to committee members, if you don't mind one second, what is "substantial evidence of benefit," just so that we're clear.

DR. PAZDUR: We defined it in your preamble, if you care to read it, okay, to avoid any problems.

(General laughter.)

DR. PAZDUR: Do you want me to read it?

CHAIRPERSON HUSSAIN: Yes, please.

DR. PAZDUR: "In general, substantial evidence requires at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. The requirement for more than one trial reflects the need for independent substantiation of the experimental results.

"Substantial evidence also may be provided by the results of a single adequate and well-controlled efficacy study when a single multicenter study of excellent design provides highly reliable and statistically persuasive evidence of an important clinical benefit, such as an effect on survival, such that a confirmatory trial is not ethical.

"In all cases, it is presumed that a single

study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal, and that the results reflect a clear prior hypothesis documented in the protocol."

In essence, that is what we mean by "substantial evidence."

CHAIRPERSON HUSSAIN: Thank you.

If the FDA has no additional clarifications to make, and if the committee members have no questions to ask or clarifications to seek, we can actually begin with the voting process.

I'm sorry. Go ahead, Dr. George.

DR. GEORGE: A question or some clarification or maybe just a comment, let's see, what slide is it? The Sponsor's Slide 56 I think is probably the best place to look at it where it is pooled results for overall survival in the 2006 data.

(PowerPoint presentation is in progress.)

DR. GEORGE: I still don't know if I've had a good answer about the followup. With respect to

survival, the trial completed accrual 10 years ago, and in the potential followup for all patients would have been between 9 and 13 years.

If you look at the tick marks on these curves, which are patients still alive at last contact, there are a substantial number. Now, in general, if you assumed that there was no sort of random sensoring, that wouldn't be so bothersome.

But some of the things I've heard today have bothered me somewhat about whether there is a potential anyway for some kind of non-randomness that's sensory.

In which case, I'm a little surprised. I know a lot of effort went into this preparation of this package and everything, I'm just a little surprised that there wasn't more effort to get those tick marks moved to the right, if they can be.

My looking at this, I heard various figures about completeness of followup. But as of 2006, it is not all that complete, particularly if you look at it's not really true that no one dies after five years, for example. I'm still worried about that.

In some ways, it is a subsidiary question

because the main emphasis is on disease-free survival. A lot of emphasis was put on the fact that there is a survival impact as well even doing this kind of analysis.

I don't know if it is really a question. Probably, people have answered it as well as it could be answered already, but I'm a little bothered by this, the number of tick marks, the earlier periods of time where there is still some risk of dying.

CHAIRPERSON HUSSAIN: Dr. Mills and then Dr. Lu.

DR. MILLS: Thank you. I think that I didn't mean to imply that there were no events after five years, but that the majority of events occur in five years.

We are focusing our efforts on getting the additional followup, first, for patients who have less than five years at last contact, but we have a list actually of every patient who had a sensor date prior to the 2003 dataset that we are also trying to get that information for.

I think it is also important to show you it by

four arms and remind you that the two MTP arms are the two on top, that we are not talking about an interaction here.

Then, finally, that survival is not random, but it is actually very even across the arms we've looked at. We were concerned about whether it was even across the arms, and in fact it was quite even across the arms. We are focusing on the less than five years, but again we will focus on every one who had a sensor date prior to 2003.

CHAIRPERSON HUSSAIN: Dr. Lu.

DR. LU: Yes. To further clarify the question, I would like the members to look at Table 11 on page 25 of the briefing document, FDA's briefing document.

When you look at the table, you could see that 10 percent of the patients, among those 505 remaining patients who were alive as of last contact there were 10 percent with last contact on or before December 31, 1998, and 26 percent with last contact on or before December 31, 2000. Forty-three percent of those patients were alive with last contact on or before

December 31, 2002.

DR. MILLS: It is important I think to distinguish whether we are talking about the 2003 or 2006 dataset. I was referring to the 2006 dataset.

DR. LU: It'S 2006.

DR. MILLS: That was the 2003, wasn't it?

DR. LU: No, 2006.

CHAIRPERSON HUSSAIN: I think I'm going to ask that we move ahead with the vote. That's the last comment we're going to take right now.

DR. ADAMSON: If we were to take at face value the last slide we looked at where, again, I come back to a very clear disconnect between survival and disease-free survival, where the survival analysis, if accurate, suggests that there is benefit to MTP-PE.

The question is why would there be a disconnect between disease-free survival and survival, if this is the case? How should we or should the company begin to evaluate everything that happens after a first event in patients with osteosarcoma? I will throw that out to anyone in the company, Dr. Kleinerman or Dr. Meyers.

If my assumption is correct that there is a disconnect between the survival analysis and the disease-free survival analysis, why would there be that disconnect, and how confident can we be of what happens after first event that will impact survival?

DR. MEYERS: Peter, I think I would answer that question two ways. The first answer that I would like to make is that disease-free survival is subject to a variety of ascertainment biases, which are not a factor in ascertainment of survival.

The second is that we conclude that there in fact is a benefit in DFS and that benefit is confirmed by the presence of the benefit in overall survival. You are concerned by what appears to be an interaction. We have a difference of opinion on that, but there is no suggestion of an interaction in survival.

Finally, what happens to patients after recurrence in osteosarcoma is well documented in multiple publications. We know that number, one, the application of chemotherapy does not affect survival post-occurrence in osteosarcoma.

We know that if you don't do surgery after

recurrence in osteosarcoma, you will not survive. We know that the presence of metastases outside the lungs have an impact on the survival after recurrence.

We looked at the factors which do contribute to recurrence, the post-recurrence survival, that includes the site of recurrence and the frequency of surgical attempts at recovery.

They are not different between arms, which leads me to conclude that it was the application of MTP and primary therapy that contributed to the improved survival.

DR. LEWIS: I just want to comment from an external viewpoint here really, and that is to say that early on when I started I said that my preconceptions have been changed about the agents and about why it had been changed.

I think that the data we saw early on, admittedly the disease-free survival data from 2003 were too early data. It is early data that actually doesn't pass the test that we would apply within the European Osteosarcoma Intergroup where survival is the key endpoint and would be seen as the key endpoint along

side other forms of endpoint like progression-free survival, which is our preferred method. It is actually the overall survival data that has convinced me of the benefit of this drug.

Now, we don't know a lot about how many of the drugs that we use work or how they have an overall benefit. What I am clear about is that surrogate markets being used to decide whether a drug does or doesn't stand or fall for its future are not appropriate if you have overall survival there.

We have overall survival here showing no evidence of an interaction between the arms. The last thing was compelling for me and has been compelling for my colleagues in Europe.

CHAIRPERSON HUSSAIN: Thank you, Dr. Lewis.

We are going to go to the vote now. If you can, have the question up again, please.

(Staff complies.)

CHAIRPERSON HUSSAIN: We are going to begin on my left with Dr. Reaman. Please, for all the voting members on the Committee, turn on your microphones, speak clearly for us so it can be recorded, identify

yourself. We will not be taking comments about the vote. It's a yes or no vote.

Thank you.

DR. REAMAN: Reaman, no.

DR. GEORGE: George, no.

DR. D'AGOSTINO: D'Agostino, no.

DR. PERRY: Perry, no.

DR. RICHARDSON: Richardson, no.

CHAIRPERSON HUSSAIN: Hussain, no.

DR. MORTIMER: Mortimer, no.

DR. RODRIGUEZ: Rodriguez, yes.

DR. HARRINGTON: Harrington, no.

DR. HAYLOCK: Haylock, yes.

DR. MYERS: Myers, No.

DR. ADAMSON: Adamson, no.

DR. HELMAN: Helman, no.

CHAIRPERSON HUSSAIN: Dr. Blaney, please vote.

DR. BLANEY: No.

CHAIRPERSON HUSSAIN: Dr. Blaney is a no. On the question that is posed to us by the FDA, there is a no vote, twelve; a yes, two. I think that is the only question we have here. Thank you. I

just want to remind the Committee that what we are voting on is not approval or disapproval. This is a vote on the question that is posed to us by the FDA. Thank you. We will adjourn now and we will reassemble again at one o'clock for the second hearing. Thank you. (Whereupon, at 11:44 p.m., a luncheon recess was taken, to reconvene this same date and place at 1:00 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:00 P.M.)

CALL TO ORDER

CHAIRPERSON HUSSAIN: Please take your seats. We are going to begin this afternoon session. I am Maha Hussain, and this is the afternoon ODAC meeting to discuss an NDA proposed for an agent called OrBec® by DOR Bio Pharma. I would like to begin first by welcoming you all and start with Dr. Link, around the table, to get the committee members introduced with names and affiliations.

INTRODUCTION OF COMMITTEE

DR. LINK: I'm Michael Link from Stanford

University. I'm a pediatric hematologist/oncologist.

MS. HAYLOCK: Pamela Haylock, oncology nurse and consumer representative.

DR. HARRINGTON: Dave Harrington, statistician, Dana-Farber Cancer Institute.

DR. RODRIGUEZ: I'm Maria Rodriguez, medical oncologist, MD Anderson Cancer Center.

DR. MORTIMER: Joanne Mortimer, medical oncologist, University of California, San Diego.

MS. CLIFFORD: Joanna Clifford, designated federal official to the ODAC.

CHAIRPERSON HUSSAIN: Maha Hussain, medical oncologist, University of Michigan.

DR. RICHARDSON: Ron Richardson, medical oncologist, Mayo Clinic, Rochester, Minnesota.

DR. PERRY: Michael Perry, medical oncologist/hematologist, Ellis Fischel Cancer Center, University of Missouri, Columbia, Missouri.

DR. SPORTES: Claude Sportes, National Cancer Institute, pediatric hematology/oncology and transplant.

DR. FLATAU: Art Flatau, I'm the patient representative from Austin, Texas.

DR. SHAN SUN-MITCHELL: Shan Sun-Mitchell, stat reviewer, FDA.

DR. SRIDHARA: Rajeshuari Sridhara, statistical team leader, FDA.

DR. SCHER: Nancy Scher, clinical reviewer, FDA.

DR. FARRELL: Ann Farrell, clinical team leader and acting deputy director.

DR. JUSTICE: Robert Justice, director, Division of Drug Oncology Products.

DR. PAZDUR: Richard Pazdur, office director.

CHAIRPERSON HUSSAIN: Thank you. Ms. Clifford will read the "Conflict of Interest Statement."

CONFLICT OF INTEREST STATEMENT

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and

Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 21 U.S.C. 355 and 4, a waiver has been granted to Dr. Maha Hussain for owning stock in two competitors worth between $5,001 and $25,000 per firm. This de minimis financial interest falls under 5 C.F.R., Part 2640.201, which is covered by regulatory waiver under 18 U.S.C.208(b)(2).

A copy of the waiver statement may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12-A30 of the Parklawn Building.

Waiver documents are also available at FDA's dockets webpage. Specific instructions as to how to access the webpage are available outside today's meeting room at the FDA information table.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted

for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they wish to comment upon.

Thank you.

CHAIRPERSON HUSSAIN: I would like to invite Dr. Schaber to begin the discussion from the Sponsor.

Sponsor PRESENTATION

INTRODUCTION AND BACKGROUND

(PowerPoint presentation is in progress.)

DR. SCHABER: Madam Chair, members of the committee, ladies and gentlemen, good afternoon. My name is Chris Schaber. I am the president and chief executive officer of DOR Bio Pharma.

On behalf of Dor, our clinical investigators, and our patients I would like to thank the Committee and the FDA for allowing us the opportunity to present our OrBec clinical data in the treatment of acute graft-versus-host disease or GVHD, which is the primary cause of early morbidity and mortality following allogeneic hematopoietic cell transplantation.

By way of agenda, I will be providing a brief introduction and overview of OrBec or beclomethasone dipropionate and then turning the presentation over to our lead presenter, Dr. George McDonald, who will present on acute graft-versus-host disease, our clinical data, and finish with a benefit/risk assessment.

Dr. McDonald is professor of medicine at the University of Washington and head of gastrointerology at the Fred Hutchinson Cancer Research Center. Dr. McDonald has pioneered the use of oral beclomathasone dipropionate in the treatment of acute graft-versus-host disease.

Dr. McDonald has also been instrumental in working with the company as both a clinical advisor and consultant in moving the program forward to where it is today.

Moderating today's Q-and-A session will be Dr. Tim Rodell, medical monitor for the Phase III clinical study.

Our external advisors: Dr. David Hockenbery, a member of the Fred Hutchinson Cancer Center and lead investigator for the Phase III clinical study, Study ENT

00-02; Dr. Ted Gooley, also from the Fred Hutchinson Cancer Research Center and lead statistician for the Phase II clinical trial, Study 875; as well as Dr. Keith Sullivan, chief of medical oncology and transplantation at Duke University Medical Center.

Dor Bio Pharma is a biopharmaceutical company focused on treating life-threatening side-effects of cancer treatments and serious GI diseases.

You may have read in your briefing document the company named Enteron Pharmaceuticals. This is the company that acquired the technology from Dr. McDonald and is a wholly subsidiary of Dor Bio Pharma.

The active ingredient in our drug product, beclomathasone dipropionate is a potent synthetic corticosteroid with strong antiinflammatory and immunosuppressive properties widely used and marketed in a number of topical applications.

The nomenclature you will be hearing today, "BDP" or "beclomathasone dipropionate" or "oral BDP, which is the drug product formulation, which consists of two tablets: an immediate-release IR tablet of 1 milligram to treat inflammation of the upper GI, and a

delayed-release, enteric-coated tablet of 1 milligram to treat inflammation of the lower GI.

It is this two-pill system which makes up the therapy, two tablets or 2 milligrams given 4 times a day, for a total of 8 milligrams per day over a 50-day treatment period. OrBec® is the proposed trade name for oral BDP.

Oral BDP development began in 1991 under an investigator-initiated IND at the Fred Hutchinson Cancer Research Center. With the support of orphan drug grant monies, the clinical program moved forward, namely, with the conduct and execution and completion of a Phase II blinded, randomized, placebo-controlled trial in 1998, Study 875.

We received "orphan drug" designation due to the fact that this is a small patient population being treated of about 7,000 patients annually in the U.S. Ownership of the application was transferred in 1999 to Enteron Pharmaceuticals to move forward with the conduct of the Phase III clinical program.

"Fast-track" designation was also granted due to the fact that there is an unmet medical need that

exists with this disease.

In 2005, we completed the pivotal Phase III clinical trial under a special protocol assessment, or "SPA," with the Division of Gastrointestinal and Coagulation Drug Products. This was Study ENT 0002.

Shortly after completing the study, the application was transferred from gastrointestinal to oncology drugs. We filed our new drug application in September 2006.

We have conducted four clinical studies using oral BDP in patients with GI GVHD. The two we will be focusing today's presentation on are the blinded, randomized, placebo-controlled trials, Study 875, which is a Phase II single-center trial in 60 patients, and Study ENT 0002, a Phase III multicenter pivotal study in 129 patients.

Although we did not achieve statistical significance in the primary endpoint of our Phase III clinical trial, we believe approval is merited based on a favorable safety profile and clinical benefits as measured by reductions in GVHD treatment failure.

Obviously, with treatment failure comes a

higher dose of systemic corticosteriods needed, mortality at transplant day 200, and mortality at one year post-randomization.

The proposed indication for OrBec or oral BDP is for the treatment of graft-versus-host disease involving the gastrointestinal tract in conjunction with an induction course of high-dose prednisone or methylprednisolone.

It is our hope today that once the Committee hears the OrBec clinical story, you will all agree that there is an important role for this drug to play in the clinicians arsenal in the treatment of this orphan disease.

With that, I would like to turn the presentation over to Dr. McDonald who will review acute graft-versus-host disease as well as our clinical data.

Again, I would remind everyone that the moderator for today's session will be Dr. Tim Rodell, medical monitor for the Phase III clinical trial.

Thank you. OrBEC FOR THE TREATMENT OF GRAFT-VERSUS-HOST DISEASE

(PowerPoint presentation is in progress.)

DR. McDONALD: Thank you, Dr. Schaber.

I am George McDonald. By way of disclosure, I will tell you that after the FDA's Division of Orphan Drug Products granted orphan drug designation for this drug for GVH I licensed that along with a utility patent that I had received to Enteron Pharmaceuticals.

I am a consultant to Dor Bio Pharma, and I have an equity position. Please note that I recused myself from participation in all trials following this licensure agreement.

I'm going to talk a little bit about the disease, graft-versus-host disease. This is the focus of the two randomized trials. This is an inflammatory multisystem disorder, a complication, if you will, of allogeneic transplantation.

The pathophysiology is the attack of donor immune cells and release of cytokines in host tissues. The traditional target organs are the gastrointestinal tract, the skin, and the liver.

We now know that the list of organs is larger than this. We know that there is kidney involvement and especially pulmonary involvement in graft-versus-host

disease.

The traditional grading system grades this disease from one to four. This grading system is based on various combinations of GI, skin, and liver involvement. This affects approximately 60 percent of allogeneic graft recipients, roughly, 7,000 patients a year.

Now, among patients with Grade I to IV graft-versus-host disease, that is, GVH requiring treatment, the majority now have Grade II graft-versus-host disease.

Advances in the transplant field have fortunately reduced the frequency of severe, fatal graft-versus-host disease to a relatively small number. The focus of today's presentations is in patients with Grade II graft-versus-host disease.

The designation as Grade II implies that this is somehow a mild disease, but these are data from two multicenter randomized trials of patients with GVH looking at prophylaxis.

Among patients with Grade II in both trials, there is a 25 percent mortality risk. Grade II implies

a less severe disease, but this is a disease that carries a penalty.

I also note that the disease itself is not causing this mortality. No one dies from Grade II graft-versus-host disease. The deaths are due to the treatment, that is, high-dose prednisone and severe immunosuppression.

A brief timeline for transplant, just to give an orientation. The conditioning therapy of a myeloablative nature, that is, one that ablates the hematopoietic and immune systems, is given before day zero when donor cells are infused.

The standard GVH prophylaxis consists of a calcineurin inhibitor, cyclosporine or tacrolimus with intermittent methotrexate. The calcineurin inhibitor is discontinued if patients are doing well, free of GVH, usually at day 70 to 80, but the calcineurin inhibitors are continued if there are active signs of GVH.

Notice that these landmark endpoints, day 200 is the traditional transplant literature endpoint for the end of immunologic hostilities due to GVH.

Certainly, the immunologic fires of graft-

versus-host disease are usually over by day 365. Acute GVH can appear anytime from day 12 to 15 out way past day 200.

Following its appearance, there is the potential for high-dose prednisone use, and inevitably the infections that result from severe immune suppression.

I'm going to talk a little bit about non-myeloablative conditioning regimens, the shorthand mini-transplant has now been replaced by reduced intensity regimens.

But the only differences here are the conditioning therapy is not myeloablative and a slightly different GVH prophylaxis is used combining a calcineurin inhibitor with mycophenolate mofetil.

Depending on what center one is at, these drugs, particularly the mycophenolate mofetil, are reduced in dosage to bring on graft-versus-host disease, hoping for an anti-leukemia graft-versus-leukemia effect.

Again, GVH can appear any time, somewhat later after non-myeloablative therapy, high-dose prednisone

and infections is the usual thing that happens.

A little bit about the gastrointestinal involvement with GVH. This is an old-fashioned barium contrast study, and I show it to illustrate that this disease affects the gut from the stomach all the way through the entire small intestine and all the way through the colon.

Early on, the dominant feature here is mucosal edema, that is, this isn't an ulcerative disease to start with. This is an inflammatory disease characterized by mucosal edema.

The symptoms are a complete loss of appetite, nausea, persistent vomiting, and diarrhea. What this looks like through an endoscope is illustrated here.

This is the stomach, that's the pylorus. You don't see ulcers. You see mucosal edema as a reflection of this inflammatory process. This is a similar process in the small intestine.

Now, the traditional treatment for GVH starting 30 years ago has been high-dose prednisone. This is a 2-milligram per kilogram per day regimen given for two weeks.

In people who have responded to this therapy, a very slow, progressive decline in prednisone doses given over a seven- to eight-week period of time. Two purposes of this, to prevent flares of the GVH once you have controlled it, and then to allow recovery of the adrenal axis.

Some 10 to 15 years ago, it was recognized that not all graft-versus-host disease is created equal. There are some that are less severe. In many centers, those less severe cases are treated with a 1 milligram per kilo per day schedule, two weeks, followed by a taper, followed by discontinuation.

This is an idealized schedule. Patients who do not respond after two weeks have their prednisone dose continued, patients who flared during this taper have a bump in prednisone that goes back up to where it was. This is a considerable amount of prednisone burden across time.

What is the penalty that you pay for this much prednisone? We know that prednisone is an effective therapy for GVH, but it is also the cause of death in patients with GVH.

Here is a study looking at CMV-specific immune responses, CD4 and CD8. In patients on no prednisone, these were normal in 74 percent and 62 percent of patients.

Prednisone less than 1 per kilo, 57 versus 50 percent had normal function. Prednisone 1 to 2 per kilo at any time before day 80, complete abrogation of T-cell responses to CMV-specific antigens.

The clinical part of that is illustrated here. These are two different studies, one looking at the risk of CMV infection by prednisone dose. The higher the prednisone dose, the higher the risk of CMV infection.

The risk of invasive aspergillosis which has become I think the dominant fatal infectious disease in these patients is also similarly related to how much prednisone a patient is exposed to.

What is the rationale for oral BDP? We know that gastrointestinal involvement predicts the outcome of GVH. This appears to be the driving organ that predicts the prognosis. This is true in animal models, and it's true in humans.

We know from 30 years of experience that prednisone therapy is effective, but there are many complications from prolonged use. We also know that oral topically active corticosteroids have been used safely and effectively in other inflammatory diseases.

I come from the world of gastroenterology. We have treated ulcerative colitis and Crohn's disease and eosinophilic gastroenteritis and a whole variety of inflammatory processes with these topical corticosteroids for a very long time.

In fact, the FDA has already approved 15 years ago a very similar drug, budesonide, in an enteric-coated capsule to delivery to the terminal ileum, so there is already an approved topical corticosteroid that is marketed for Crohn's disease.

It couldn't be used in these studies. As I said, GVH is a PAM-intestinal illness and a medicine targeted at just the ileum misses half of the intestinal tract. Thus, the formulation that we are going to be reporting on of an upper-intestinal release and a mid-gut release to try to cover the whole gut mucosa.

What are the expected clinical benefits? I

started these studies 16 years ago. It seems like only yesterday, but here was my expectation coming from the world of gastroenterology with th is idea for treating GVH.

We thought that BDP could maintain GVHD in remission without flares. We would put the medicine where the disease was. The expected benefit of that was decreased prednisone exposure. The expected benefit of that was decreased prednisone adverse effects and preservation of immune function.

I want to emphasize prednisone adverse effects are not just the infections. The patients who take prednisone vividly remember usually the insomnia, the anxiety, and many of the physical attributes that come from prolonged prednisone exposure. Finally, it would naturally follow if these three things happened that there would be better outcomes.

I will now discuss the two randomized placebo-controlled trials. We first, before we started the randomized trials, did Study 615. This established that the oral root for beclomathasone was well tolerated.

There did not appear to be substantial safety

