of data cutoff for submission of this application, 241 patients had been enrolled of which 237 had actually received treatment. This was perfectly balanced between the two arms. Of the 237 patients receiving treatment, 81 or approximately 1/3 were found to be both platinum and paclitaxel resistant.

Of those 81 patients 44 were in the Doxil arm and 37 in the topotecan arm. Of the 37 in the topotecan arm, three responded for a response rate of 8.1 percent. In the Doxil arm of the 44 patients refractory to both drugs, six responded for a response rate of 13.6 percent.

In this case we have chosen just the Doxil arm as this was not intended to be a comparative study at the time of interim analysis. The 95 percent CI ranges from approximately 5 to 27 percent.

Combining then all of the Phase II studies plus the Doxil arm of the Phase III study, we derived a response rate of 13.8 percent with 95 percent CI ranging from 9.2 percent to 19 percent for Doxil.

In terms of the safety review, this slide and those following it will focus on the organ system

that was affected by Doxil therapy. In this case the manifestations of the cutaneous toxicity of Doxil are grouped cutaneously.

Specifically you've heard previously about the Palmar-plantar erythrodysthesia that under the three week schedule was in excess of 80 percent. That had been reduced down to approximately 40 percent in the three four-week schedules; that is, 30-47, 30-47E, and 30-49 Doxil arm. Other manifestations of the cutaneous effects of Doxil include rash, exfoliative dermatitis, vesiculobullous rash.

This graph shows essentially the same data but for the mucous membranes manifesting itself as mucositis and stomatitis. Asthenia didn't fit well into any of the categories.

The third grouping of toxicities was that of mild suppression. Neutropenia was found to be present in approximately 50 percent of incidents in the three week schedule that had been reduced somewhat down to 37 percent in the four week schedule. The same for leukopenia, anemia, and thrombocytopenia.

In study 30-47 there were patients that

required both red cell and platelet transfusions, although there were no significant hemorrhagic consequences of the thrombocytopenia.

Lastly, this graph illustrates the gastrointestinal adverse effects of Doxil; nausea, vomiting, anorexia, and diarrhea. The sponsor states in their study report that with current 5HT3 antagonism that nausea and vomiting should be completely medicable.

This last graph demonstrates the adverse events under the four-week schedule using study 30-47 that was reviewed carefully by the Food and Drug Administration. In this instance, the six most common adverse effects which corresponds to that in the questions to the committee are Palmar-plantar erythrodysthesia, astenia, anemia, nausea, neutropenia, and stomatitis.

In blue is shown the relative frequency of each of these adverse events. In red is the frequency of serious adverse events. Serious adverse events in this case were defined as grade IV hematologic toxicity and grade III and IV nonhemotologic toxicity.

Note that the serious incidents of PPE is significantly less, although it is still approximately 20 percent and can be anticipated to be so under the proposed schedule.

In terms of summary, the sponsor has submitted three Phase II trials, one Phase III trial. The one Phase III trial has again close to accrual but is still maturing. In one of the Phase II trials they are still maturing as well. A 13.8 percent response rate was determined by the agency combining the Doxil arms of the four submitted studies. There was one Phase II trial that revealed no responses.

In terms of the safety summary, clearly the four-week schedule is less toxic than the three week schedule. The adverse events can be grouped in terms of cutaneous and mucocutaneous events, hemocological, and gastrointestinal toxicities. Asthenia was frequent as well. Some of these adverse advents, while not necessarily highly frequent, are quite serious.

So we return then to the question that we started with. Does the committee feel that the

objective response determined from these trials indicate that Doxil is reasonably lucky to be associated with clinical benefit in this population.

DR. DUTCHER: Are there questions from the committee? Dr. Ozols.

DR. OZOLS: On your review of the response and efficacy, do you have any impression or analysis of who you think may benefit and who we should or shouldn't treat?

DR. FRYKMAN: Yes. We had done a significantly expanded analysis over that of the sponsor. It is clear that there are anecdotes of patients that actually have large bulk disease. Again, these are spotty anecdotes where there was actually a significant response seen. Not necessarily a CR but an occasional PR were noted.

Otherwise, it appears from what the sponsor presented and in the briefing document that, again, patients with apparently more aggressive disease, i.e., younger, perhaps those with a higher CA-125, were associated with a poor response rate.

Perhaps in terms of advanced histologic

rate or more poorly differentiated histologic rate, tumor bulk, perhaps younger age, and perhaps even a significant degree of prior treatment, I would think those factors would be taken into consideration. But the strength of the association I would not be able to comment on.

DR. OZOLS: The other question is, you know, the years -- I mean, I certainly haven't seen many presentations here where you had clinical trials presented by a sponsor which from different groups or different agents or different parts of the country or the world which I'm sure has different results.

I'm still concerned that we've got one large trial from Europe which is failing to show any possible reasonable clinical benefit when they have zero out of 36 and they are still going on with more patients. Do you have any sense of -- two things. Have you ever seen this kind of thing before or do you have any sense why this particular study is negative?

DR. FRYKMAN: As far as experience goes, my experience is quite limited. I probably wouldn't be able to comment too intelligently on that. I would

make somewhat of a statistical comment. I'm sure Dr. Simon will have more to say than I.

If you look at the 95 percent confidence interval, and if you assume it to be the fact that if this trial were repeated 100 times, 95 percent of the time the results would be within that 95 percent CI, that in fact, albeit unusual, the response rate noted in study 30-47E which was zero, although the CI ranged from zero to 9.7, in study 47, which ranged from something like 30 percent down to 9.7, that those 97 percent CI's actually do overlap. While it would be an unusual occurrence, within our understanding of statistics, it is actually a possibility. That is, they do return something close to the same response rate.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: Given the bias issues that we discussed yesterday and the well recognized difficulty of measuring ovarian cancer, are you quite confident that in terms of the actual data everything is clean and the responses were real responses and there were no issues there?

DR. FRYKMAN: Yes. Well, here's how I can answer this question. We were not presented with the primary radiographic data so we relied on the sponsors primary electronic data of tumor measurement dimensions. That is, there may have been one, two, or three lesions each with these dimensions and from that table we could confirm the responses that we showed up here.

The translation going from the radiographic data to the autronic data, there is always some question about it. Now, to the sponsor's credit they also underwent an independent radiological review. For the most part those were confirmed. Not in every case but for the most part those were confirmed. That gave us actually reasonably good confidence that an independent body of a radiologist and a gynecological oncologist actually did come to quite close conclusions.

DR. DUTCHER: Dr. Nerenstone.

DR. NERENSTONE: I just had a question about the first study. Only three cycles were to be given and that would be even with delays 12 weeks.

The median time to response was really in most of the groups beyond that. Were there people who were stable at the end of those three weeks who then went on to respond and were they counted in the numerator of responses or was it only at the time after those three cycles that you got the responses?

DR. FRYKMAN: During the review of both 30-22 and 30-47 the response was counted at the time the response occurred. If it was confirmed, then we had data within four weeks or so.

If a response occurred and we didn't see a subsequent response or the response maintained and we didn't count that, what I can say is in the cases of a response in 30-22 even thought the duration of therapy was relatively short compared to the other studies, if a response was confirmed within the time period that the data was sent to us by the company, then that was counted.

DR. DUTCHER: Dr. Schilsky.

DR. SCHILSKY: Greg, I wanted to just come back to a question that I think Bob Ozols raised earlier. I'm still a little bit confused in terms of

how the definition of refractoriness was applied. There was a grand total of 26 responders across all of these studies. I guess the question would be of those 26 individuals who responded, do you have a sense of how many of them had been shown to be refractory to a platinum paclitaxel combination as opposed to be refractory to a platinum-based regimen followed by a paclitaxel-based regimen?

DR. FRYKMAN: Yes. So in studies 30-22 the eligibility criteria for the refractoriness was exactly as suggested. In other words, they could be in sequence or together. When the study was done, paclitaxel was not on the market yet and so this came on subsequently.

In terms of 30-47 I believe that also had the same criteria although you could see the change in the standard of care over the time period of study 30-22 to 30-47. In fact, this is speaking off the top of my head, I would say the majority of the responses or of the patients that were considered eligible in 30-47 had actually been concomitantly treated with both paclitaxel and either carbo or cisplatin.

Not necessarily six cycles in a row but these patients may have been treated with platinum up front and then got hexomethomellomin and then gotten something else, PP16, they still recurred, and then they got combination platinum and paclitaxel.

DR. SCHILSKY: What I'm trying to get at is, you know, if this drug is on the market and with contemporary management of ovarian cancer usually beginning with a platinum paclitaxel combination, for women whose disease is clearly refractory to that combination. What is the likelihood that if those women were treated with Doxil that they would respond? Is there any way we have of estimating that?

DR. OZOLS: That's what I asked them, to see if they could get that information; did you ever have a response to somebody who did not respond to something else in the past.

DR. SCHNIPPER: I can show you if you would like.

DR. DUTCHER: Go ahead.

DR. SCHNIPPER: If I could have the slide on, please. As was correctly stated, in 30-22 many of

the patients were treated in sequence because of the treatment guidelines at that time. By the time the trials evolved, most of the patients were, in fact, treated with platinum and paclitaxel in combination. Of the 146 patients on the overall refractory database, 115 were treated in combination of which 19 responded.

The response rate in patients who received platinum and paclitaxel in combination was 16.5 percent compared to its sequential, keeping in mind that the sequential population may have had up to five regimens prior to having Doxil.

DR. OZOLS: Right, but those who received the combination could have responded initially then progressed and then gotten Doxil. The question is those who received the combination up front and did not respond.

DR. SCHNIPPER: We were looking at that over the break and there were at least four patients of the responders who had primary refractoriness to their initial combination.

DR. OZOLS: Okay.

DR. DUTCHER: Other questions for FDA? Dr. Santana.

DR. SANTANA: When you reviewed the data set, did you get an idea of these patients that developed PPE how severe this was in relation to having to add concomitant meds to control the symptoms?

DR. FRYKMAN: Um, yeah. The study 30-47 again should be reviewed in detail. Also included with it is a health care quality of life questionnaire which was piloted by the company and was not intended for efficacy or safety purposes. In fact, it was quite illustrative. During the review of the case report forms, this data had not necessarily made it into an easily readable form in the electronic data so, in fact, I had the luxury of having each CRF and could go through and look at both what the patient should do as well as what the patient's own feeling about her disease was at the time of being seen. Some of these patients were being seen every four weeks and we had health care quality of life data on them.

To a certain extent ut was like actually

having the patient in the examining room where you could ask them questions. "How are you feeling? How are you walking around?" Sort of what's up. The dose reductions that were carried out by the physician clearly correlated with the woman saying, "Gee, it hurts a lot to walk on my feet. They are blistered." Or, "Gee, I'm feeling fine. I'm on my night cycle of Doxil and I have very few complaints."

I would say that actually the health care quality of life was very illustrative for me and for probably other people that have looked at the data. We didn't do any statistical correlations but it was clearly correlated.

DR. SANTANA: My question was more simple. How many of these patients required aggressive narcotics use, aggressive analgesic use, etcetera?

DR. FRYKMAN: I can't tell you that specifically with respect to PPE. We did obviously have all the concomitant medications. It would have required us to correlate each date of the medication given with what was the symptom at the time.

The first attempt was to obviously delay

therapy. If that wasn't helpful, then the patients had their dose of Doxil reduced. To what extent they got concomitant medications for the PPE, I guess, I wouldn't be able to comment on direction.

DR. DUTCHER: Does the sponsor have any information on that?

DR. GORDON: I can't give you exact numbers in terms of --

DR. DUTCHER: Would you state your name?

DR. GORDON: I'm sorry. I'm Alan Gordon with the Sammons Cancer Center. We treated a vast majority of the patients on the 47 trial and for the most part most of the patients required no concomitant medication. It was just a matter of watchful waiting and it would gradually resolve. There were occasional instances of maybe some mild analgesics being administered but never any narcotics were required.

DR. DUTCHER: What was the time table for the resolution of the symptoms? How long did you wait between cycles?

DR. GORDON: Most of the waits were at most a one-week delay. There was a rare patient that

may have gone beyond one week. I can't recall anybody specifically going beyond a one-week delay in recovery.

DR. DUTCHER: Any other questions for FDA? Thank you very much. Before we go onto the discussion we do have one person for the open public hearing. Is Susie Bendel here? Just state your name and your affiliation and whether there is any financial support for your appearance.

MS. BENDEL: My name is Susie Bendel. I work for a private physician at the Washington Clinic. I have no financial to ALZA or anybody else.

I originally started with Doxil on the breast study. It was a taxene resistant study. We used a smaller 30 milligram per meter squared dose. Our side effects -- what I really want to point out to the FDA that the side effects are really manageable as long as the nurses and the physicians are aware of them.

As far as the infusion reactions, those are very well managed by stopping the infusion and rechallenging. There's not a problem with that. The

patients usually become very flushed first so you immediately can stop it before shortness of breath or the patient becomes anxious.

I'm sure the reason some of the patients went off trial is because they got the shortness of breath and they didn't want any further treatments. If you see the redness in the flushing of the face, you know automatically to stop the treatment and just flush and then rechallenge them and they do find.

As far as the Palmar-planter, we had only one and that was after the patient had received almost 12 months of treatment. As I said, that was at 30 milligrams per meter squared. It was very mild. It was in the winter time actually and the patient had gone outside without wearing gloves and she did get very cold. We encourage our patients to avoid any frictions and things like that and to avoid hot or cold.

If the patients are acknowledged and the staff is acknowledged, there shouldn't be a problem with any of the reactions you guys have discussed today.

DR. DUTCHER: Thank you.

MS. BENDEL: Thank you.

DR. DUTCHER: Any initial discussion?

DR. SLEDGE: Actually, could I ask a question of Bob? If we compared Doxil to doxorubicin in this setting, what would you expect to see with doxorubicin in a refractory setting like this?

DR. OZOLS: Baseline of probably just essentially noise. I don't think you would see any activity. You would probably see an occasional response, I think. We did some studies years ago with doxorubicin as a second-line treatment in just melphalan resistant patients and we saw no responses.

There have been several other studies which have shown some responses but there have been no studies. This was before the day of taxene so we have no data at all about Adriamycin and taxene in refractory patients. I suspect it would be very, very low.

DR. SLEDGE: At least from a response standpoint this sounds like --

DR. OZOLS: This sounds higher than I

certainly would have expected to see with doxorubicin.

DR. DUTCHER: Okay. Can we turn to the questions. This application seeks accelerated approval of Doxil for the following indication. The treatment of patients with metastatic carcinoma of the ovary who are refractory to both paclitaxel- and platinum-based chemotherapy regimens. Refractory is defined as a patient having progressive disease while on treatment or within six months of completing treatment.

Under accelerated approval regulations for indications where the new drug appears to provide benefit over available therapies, accelerated approval may be granted on the basis of a surrogate endpoint that is reasonably likely to predict clinical benefit.

After approval the sponsor is required to perform a Phase IV study to demonstrate the treatment with the drug is indeed associated with clinical benefit.

For this application the surrogate endpoint is objective response rate. The agency has determined that from a regulatory standpoint there is

no available therapy for the proposed indication.

The central question before ODAC is whether the findings presented in this application are reasonably likely to predict clinical benefit. The FDA analyses of response rates from three Phase II trials and the interim findings from the Phase III trial are presented in the table. The summary is as presented by Dr. Frykman of 13.8 percent response rate.

Dr. Schilsky.

DR. SCHILSKY: A question to the FDA. Do you want us to answer this question independent of whether there are any ongoing or planned trials that might be appropriate to provide the confirmatory data?

DR. WILLIAMS: Yes. We would certainly be open to your guidance if you were to decide to approve this on the basis of accelerated approval. Guidance on what sort of follow-up trial would be needed. That would be a good question to answer. Does that answer your question?

DR. SCHILSKY: Yes. It's not clear that the Phase III trial that's recently completed accrual

would be able to provide the confirmatory data for full approval. I want to be sure that if we answer this question in the affirmative, that it will be clear that there will need to be additional studies beyond the Phase III trial that are appropriately designed to provide the confirmatory endpoint.

DR. WILLIAMS: It is certainly our responsibility to make sure before an approval that such a trial is planned and committed to and we would welcome your input on what sort of trial would be necessary.

DR. OZOLS: I mean, the problem with this question about available treatments and what is community practice, I think what we would really like to see whether there is a clinical benefit of this agent. In the real world there are many other drugs that are being used. I mean, the FDA decided that available is indicative of FDA approval but that is certainly not what's out there and what people use. Drugs like gypcytamene BP16 and even taxene. A lot of people are using drugs that do have some activity in this disease.

In one sense the real measure would be to see what Doxil does against the community standard and that would be Doxil versus you decide. You pick. I don't know if the agency would like that kind of a trial or would accept that kind of a trial but that's the real world.

DR. WILLIAMS: I feel sure we would accept that sort of a trial. There was a great deal of debate on this particular application within the agency about the meaning of available therapy, whether it should be just anything in the literature or should just be what's in the label. I think we came to sort of a compromise that will be published in the form of a guidance soon. In general it's what's in the label unless there is basically a great deal of data supporting efficacy in the literature.

I think one of the reasons is I believe if you look in the literature, you will see response rates. I don't believe that this 13.8 percent response rate would be in the literature as a 1[illegible].8 percent response rate. You would never see the trial with the zero percent response rate and the others

would be inflated relative to what we see. There is some lack of fairness to say here is the FDA response rate versus what's in the literature. I think that is some of the thinking behind.

The other point is that we would like to encourage drug companies to update their label so that we have a real effective label that does include all the indications that should be in it. If the drug companies have no incentive for updating their label, then they may not. That's the thinking behind our stance. We're not asking you to make a comparison to what's out there. We're asking you to say is there or is there not reasonable likelihood that this response rate represents clinical benefit.

DR. DUTCHER: Dr. Nerenstone.

DR. NERENSTONE: I think that the sponsor has to be commended for looking at this patient population which notoriously has been under represented in clinical trials in terms of drug development. I think that, you know, we look at this 13 percent response rate and sort of shutter and say it's very low but they have carefully defined the

population that they are looking at. I think that for that carefully defined population, a 13 percent response rate is meaningful.

In terms of clinical benefit, I mean, I think we would all like to have heard more that patients who were enrolled on study and who got a response did have some meaningful changes in their life in terms of benefit of the drug. As Dr. Markman pointed out, those are often not the patients who can be put on these kinds of studies.

Anecdotally he says that he has some patients. Quite honestly as a community oncologist I also have had a patient who has responded significantly to this medication. I do think in the patient population we're looking at there is going to be clinical benefit.

I am still concerned about the toxicity and about the learning curve which the sponsor has admitted there is in terms of treatment using this drug. I am concerned because most clinical oncologists or Gyn oncologists are not going to have 20 patients to learn on. You want that first and

second patient as well cared for as the number 20th. I'm still very concerned about their doses. 50 per meter squared is probably fine to start with. I'm concerned that 50 per meter squared four weeks later is not too high.

DR. DUTCHER: Dr. Ozols.

DR. OZOLS: Yes. I mean, there are a lot of issues about clinical benefit. I'm not going to rehash those. I would feel much more comfortable about voting yes on the first one if I didn't have that European trial. Rich Simon did some back of the napkin here calculations. There is something worrisome about that trial of zero to 36 responses. That would not have been expected with a response rate of 15 percent by any stretch of the imagination.

Plus, if that does represent a worse group of patients we've seen, and it's quite common that the drug gets out into the community, that the response rate may drop because we will be treating more and more patients who are sick or have more disease.

The true benefit needs to be studied and it needs to be addressed in a post-marketing very

carefully designed study for symptomatic improvement as well. I think it should be approved at this point or accelerated but I would feel a lot more comfortable and I would be doing it with less trepidation if we didn't have that European trial.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: I was just going to say hopefully that what we would see would be perhaps a little bit of the opposite which is if an attempt can be made to study the drug in patients who have less volume of disease, the nonmeasurable patients with a carefully designed trial, we may actually see greater benefit than what we're seeing now.

DR. DUTCHER: Any other comments? All right. So question No. 1: Do the data on objective response indicate that Doxil is reasonably likely to be associated with clinical benefit in this population? All those who would vote yes? One, two, three, four, five, six, seven, eight, nine yes.

All those who would vote no? Two. You want to make a comment?

DR. SIMON: I think there was no

symptomatology data presented. I think a 15 percent response rate at that stage of disease, unless there was symptomatology data, I don't think it's likely to be associated with a survival benefit.

DR. DUTCHER: More toxicity was noted with every three-week schedule and with every four-week schedule. Consequently, only the latter schedule is proposed for approval. Toxicity attributed to Doxil in study 30-47, the largest study where Doxil was given by the every four-week schedule is outlined in the following table from the application.

Considering the efficacy discussed in question No. 1 and the toxicity described above, do you recommend that Doxil 50 milligrams per meter squared administered intravenously every four weeks be granted accelerated approval for the treatment of patients with metastatic carcinoma of the ovary who are refractory to both paclitaxel- and platinum-based chemotherapy regimens?

Any more discussion about dose? Dr. Nerenstone.

DR. NERENSTONE: What kind of package

insert can the FDA recommend in terms of the PPE toxicity in dose reductions for those physicians who are not savvy?

DR. WILLIAMS: I take it that you want us to be as careful as possible on the package insert. We will do that. It would be nice to be able to say, well, start at 40 and go up. I think we would have a hard time doing that without at least some data with efficacy by that method. We will be very attentive to maximum precautions on the label.

DR. DUTCHER: Do the current guidelines, the current package insert, do you have any feel for -- it's a much lower dose so this part of it is not in there. What about infusion reaction that was described that isn't even in the list here?

DR. WILLIAMS: We haven't attended too carefully to the labeling. We generally wait to see if we need to. We certainly will and we will take all of your comments into consideration.

DR. DUTCHFR: Yes.

DR. OZOLS: Have you started discussions about what will be the appropriate post-marketing

trial for looking at clinical benefit? I think this is an opportunity to try to design something that really looks again, as we talked yesterday, about trying to get a better idea what clinical benefit is all about.

I think it's going to be difficult in this disease with all the problems that we've talked about to really show clinical benefit. That doesn't mean we shouldn't try and I think it's going to be somewhat of a difficult study just comparing it against topotecan. I'm not sure that will establish clinical benefit.

DR. WILLIAMS: You haven't voted yet on whether to approve it but if you do, I would suggest you follow it with a discussion of the trial design recommendation.

DR. DUTCHER: All right. So we'll finish. We'll go through the votes and then we'll have a discussion because I think that clearly there is a certain level of trepidation. Although people have some comfort that there is some benefit here, I think they really want to see some more documentation of such.

We'll vote on question No. 2. Should Doxil be granted accelerated approval for treatment of metastatic carcinoma of the ovary refractory to both paclitaxel- and platinum-based chemotherapy regimens. All those who would vote yes? One, two, three, four, five, six, seven, eight, nine yes. All those who would vote no? Two.

All right. For the reasons stated -- and we appreciate the honesty of our committee in terms of their votes -- what would clinicians, investigators, patients feel is sufficient evidence for clinical benefit in either refractory ovarian or perhaps a slightly less refractory group of patients? What do you want to see? Dr. Ozols.

DR. OZOLS: Well, there is no question we would like to see some impact on survival but with the response rates that we're seeing in second-line treatment, it's unlikely that we're going to see any major impact on survival, particularly when all we're seeing is partial responses. Again, that's not indictment against Doxil. That's just indictment against the drugs that we do have available in that

situation. We just don't see enough good responses and complete responses to second-line treatment.

Survival is something that we all aim for but the only chance we're really going to have an impact on survival is realistically what we do up front with out initial chemotherapy. I think Doxil needs to be tested up front but that's separate from the indication that we're looking at.

I think the major impact we'll be looking at of a drug like this is really in the second-line situation the realistic benefit would be symptom control and improvement of symptoms, improvement of quality of life for all the reasons we're talked about in the past though they are more difficult but I think they need to be done.

I think a comparison of Doxil versus best available treatment with regard to including symptomatic patients would be the way to go and then give a good quality of life as best that we can and see if they are the real clinical benefit for that group of patients.

DR. DUTCHER: Can you get at that if you

took patients with only one prior therapy? One prior taxel-carbo regimen or paclitaxel platinum regimen?

DR. OZOLS: I'm not sure I'd worry so much about how much prior treatment they had. I think I would really worry about the fact that they had measurable and primarily symptomatic disease and see if they got better.

DR. DUTCHER: Dr. Williams.

DR. WILLIAMS: There was some comment about a lot of patients not being included because of the lack of measurable disease. Do you think there's a role for patients who are symptomatic and have elevated CA-125 and then have response of both of those? We've not accepted CA-125 alone at this point but that have simultaneous, a considerable CA-125 decrease plus a decrease in their symptoms.

DR. OZOLS: I think there is enough literature data to support the use of that group of patients for exactly that kind of a trial.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: Well, I think we also -- I'm not nearly as much the expert in ovarian cancer

that Dr. Ozols is but I think that there's a great problem with symptomatic patients in ovarian cancer which is that many of those patients require some kind of mechanical intervention to relieve their symptoms and their symptoms tend to behave in a sudden somewhat unpredictable but rapidly progressive fashion.

It's hard to make them go away with chemotherapy and we often don't try to treat them with chemotherapy. I would move this drug up to earlier use in a minimally symptomatic group of patients and try to include those patients who don't have measurable disease and try to find a way that everybody could agree to use the CA-125 and some careful definition of time to progression as the surrogate for clinical benefit in those patients. Also build in quality of life both for purposes of disease control as well as because of the very different spectrum of toxicities of the two drugs compared with topotecan.

DR. WILLIAMS: Are you suggesting there's a different standard for the use of time to progression in this disease than breast cancer?

You're even going another step further in considering CA-125.

DR. MARGOLIN: Yes, because I think the great majority of patients with this disease, those patients whom we can impact on the most are those that are the least likely to have disease you can measure. Then you end up with just that one dividable endpoint of survival that we talked about yesterday and it's probably not enough.

DR. KROOK: Having been here now for about 20 ODAC meetings I recall that there was a drug that came through for pancreas cancer that basically got approval based on a clinical benefit scale. I have not seen other sponsors use that but certainly we're in the same type of disease as difficult to measure, difficult to whatever. There are a few biomarkers which are available for that disease.

My suggestion would be that they develop some simple scale to do this, toxicity versus quality of life. We have looked at, as was discussed yesterday, lots of quality of life scales. It needs to be simple, easy, and to the point. I go back to

that presentation, although other members may remember that at least that was convincing enough to get full approval, what they did in pancreas cancer.

Again, response rates were, if I remember right, like 7 percent versus 1 percent. Yet, somehow we as a group obtained the feeling that there was a benefit to the patient. That's three years ago but it was here.

DR. DUTCHER: Dr. Ozols.

DR. OZOLS: As Gail Hayward said in her letter, and this is right and this is the most latest statistics, that 50 percent of ovarian cancer patients now are living five years. That's at all stages. If you look back in the 1960's it was 30 percent. This is a disease that is becoming more of a chronic disease. Patients are living longer and longer. I think that's where it becomes incumbent on oncologists to be able to use your treatments judiciously.

You certainly can't keep everybody on treatment over five years. That is why I think the use of CA-125 only is wrong. Sometimes you want to follow somebody who has minimal disease and no

symptoms because you want to have these patients live longer and longer with good quality of life so it's going to be more difficult.

DR. DUTCHER: Dr. Sledge.

DR. SLEDGE: Actually, having heard Kim, I'm wondering. It sounds like we're talking about two kinds of separate issues again here which is the quality of life issue versus the overall survival issue. I guess my question, Bob, would be can we define a quality of life type study or symptomatic type study in patients who have relatively good performance status? Is that conceivably possible in this disease?

DR. OZOLS: Yes. I think it is conceivably possible. It's going to have to be a randomized trial and obviously you're going to have to get some very careful selection criteria but I think it can be done and I think it's very important to be able to do that. More and more of us are doing that in clinical practice here. You are using your treatments more judiciously. People are living longer and longer with this and you have to know when to

treat and when not to treat.

DR. SLEDGE: The post-marketing study that I guess would be required to support this indication will probably not be the sort of trial that Kim is discussing, albeit that is a very important trial.

DR. OZOLS: The comparison against topotecan? Yeah. I don't have all the details of that study but just at the end of the day you're going to have two drugs that have about the same response rate and you're going to have different toxicities. I'm not sure what you're going to be able to say other than that.

DR. DUTCHER: Dr. Schilsky.

DR. SCHILSKY: I guess I'm still a little concerned about the ability to do a definitive trial with anything other than a survival endpoint. My concerns relate to the fact that the patients who are most in need of clinical benefit are the patients who are least likely to respond to the therapy.

As Dr. Margolin pointed out, often times when they have the symptomatic need, the appropriate therapy is not actually chemotherapy intervention.

It's a different type of intervention. It's really tough to pick out the patient population in whom you will be able to actually demonstrate clinical benefit in this particular disease.

I don't know what the other panel members think about the potential of survival as an endpoint. I never would have believed a drug that shows a 14 percent response rate could impact positively on survival until erindotecan came long. Obviously a different disease. Same level of activity that we saw with that drug and subsequently followed up by two randomized trials that each showed a survival benefit in an advanced disease population.

You could argue that colon cancer and ovarian cancer are two different diseases and you might not be able to anticipate demonstrating a survival benefit in ovarian cancer, although I never would have believed you could see it in colon cancer either until those two Phase III trials were conducted.

I'm wondering if, in fact, it would be possible to define a patient population. Maybe

patients who have progressed after front-line standard combination chemotherapy. I'm not sure what are the appropriate comparators. Maybe you could remind us what the label says for topotecan. What group of patients is topotecan currently indicated for?

DR. WILLIAMS: Platinum resistant, I think.

DR. SCHILSKY: Platinum resistant. Okay. So, I mean, the likelihood is that the group it is used in are the patients who are platinum paclitaxel resistant. It would seem that during a Phase III study compared to topotecan following progression or relapse after platinum paclitaxel with a survival endpoint might be possible. Where it would actually show that Doxil would win I don't know. It seems like it would at least be possible to do that trial.

DR. DUTCHER: Ms. Solonche.

MS. SOLONCHE: Dr. Ozols has mentioned whether it would be possible to do a trial that would show clinical benefit and quality of life and other issues. He answered the question saying, well, yes, we could do it. But more than that, I think we must

do it. If we aren't measuring things like quality of life or survival, then what are we doing this for?

DR. OZOLS: Yes. You know, I think you can do studies where patients which you are talking about waiting too late and then came as well and remaining through surgery. There are a group of patients who are asymptomatic but who have rapidly growing disease or progressing disease. Then you're not going to wait on that group of patients or they become symptomatic.

There are a lot of judicious patient selection that goes into it. By using CA-125 coupled with radiographic evidence of disease, if somebody who has grown in two months off treatment and you know things aren't -- that would be a patient, for example, you would treat. You wouldn't wait until something happened.

What you want to avoid is sometimes a patient with a rising CA-125 only for a year or two years. You're just wasting your chemotherapy there. Or who's got a small lesion that doesn't affect the quality of life and doesn't really grow much over a

period of time. By selecting the right patients and you know when to treat them, you could do a clinical benefit analysis in that group of patients quite easily. It can be done.

DR. SCHILSKY: You think you could not do a survival endpoint in that group?

DR. OZOLS: With available drugs we have we're still talking about response rates that are going to be in the 20 or 25 percent range at best and with clinical complete responses have that or a third of that. We saw today only one or two percent clinical complete remissions. I think clinical complete responders are going to be the only ones that will really impact upon survival. I think the quality of life and the time to progression are important endpoints in that situation.

DR. SCHILSKY: I mean, I must say given the difficulties of actually measuring lesions in ovarian cancer that we discussed already this morning, I'm even more skeptical about trying to use a time to progression endpoint. I'm not sure how you access progression.

I mean, there are going to be times when it may be obvious but there are going to be many times when it's going to be impossible. I'm real skeptical.

DR. OZOLS: Actually, with CA-125 data, again, that situation coupled with other things, that could be an indicator of progression. You could use that. Again, I'm not saying you use that to dictate your change in treatment or start a new treatment but an indicator to stop treatment.

DR. DUTCHER: Ms. Solonche.

MS. SOLONCHE: But what about patients whose CA-125 is useless? There is a large percentage of patients whose CA-125 stays the same.

DR. OZOLS: That's true. I mean, there's a subset of patients where I think the trial design can be done but it's going to be difficult. You certainly have to include that group of patients as well, but then you would have to use other measures of disease which aren't as objective.

DR. DUTCHER: Dr. Nerenstone.

DR. NERENSTONE: I think the bottom line is that this drug is going to have an impact on

survival. As Bob Ozols has pointed out, it's going to have to be used somehow in the front-line treatment because we know that's probably the only way you are going to impact on survival. All these 10 percent, 15 percent drugs in the second- and third- and fourth-line settings, we're not going to be able to show that they impact on survival in a large patient group.

DR. DUTCHER: Well, that was the argument for the discussion yesterday and we disagreed. We asked for that so I think we should ask for that.

DR. NERENSTONE: I think you have to decide on -- I think it may be disease specific. In breast cancer it may be different than in ovarian cancer.

DR. DUTCHER: I understand that but I'm still thinking that we're talking about what means that something is a step forward and how do you define that.

Dr. Margolin.

DR. MARGOLIN: I think if we truly don't think that this drug for this indication is going to translate into some kind of clinical benefit whether

that is survival. We shouldn't be voting for it because the confirmation of this will still be in the same indication.

DR. NERENSTONE: No. I think there is clinical benefit. I've seen clinical benefit from this drug. If you can actually prove that it's going to improve survival, I think that is the study that is going to be hard to prove. I think that the study suggesting looking at people who have some symptoms and seeing if there is clinical benefit to any individual patient is doable and probably worthwhile doing.

I think proving that as second-line or third-line treatment you are prolonging life when you only have a 10 percent response rate is going to be very difficult.

DR. DUTCHER: Dr. Sledge.

DR. SLEDGE: If I could ask the FDA panel members, if three years, four years from now we come back and we have a front line study that shows no survival advantage over topotecan and a second-line study that shows no quality of life advantage, then

what happens?

DR. JUSTICE: We bring it back to the committee for consideration to be taken off the market for that indication.

DR. NERENSTONE: Do you really have to show advantage or can you show equality? Because quite honestly using topo and using Doxil, Doxil has a far preferable toxicity profile. You know, if you show that they are equal, I'm not sure then you would throw out Doxil and say it's no good. Do you really have to show superiority?

DR. JUSTICE: Well, too bad Bob Temple is not here because he would love to talk about the problems of the equivalence trials but it would take a huge trial and would be very difficult to do that. I think you would have to show that you are better than the controlled therapy.

DR. DUTCHER: Ms. Solonche.

MS. SOLONCHE: My concern here is also that by giving approval and an accelerated track to this, are we setting a bad precedent in that we are accepting trials that do not show enough response rate

ad are we aiming too low?

DR. OZOLS: Well, my reading of the regulations is that accelerated approval is really raises a bar for the company now to come back and show us that, in fact, it does make a difference.

MS. SOLONCHE: Yes, but I think one problem is that the public will see this approval and maybe some clinicians as well and will think, oh, well, let's concentrate more on this drug. This is approved. It must be better than the ones that have not been approved that are used in a similar situation like gemcytabine or etopacide.

DR. WILLIAMS: Well, this company chose to proceed with this application and was the first to get accelerated approval. Perhaps it will encourage other companies to update their label. They were the first one to demonstrate it and we don't really know if these these other companies could demonstrate it. We just know that this one did. This indication is no longer available for the accelerated approval type of approval. Anybody else could come in and show clinical benefit and get the same indication.

DR. DUTCHER: I think what we have to remember is that this is a very selected population, very small numbers of patients. We often learn more about an agent once it's available for further study than we would from the initial approval trial. For example, we don't know what happened to the people that were on these trials that were not in the refractory group. They may have had a different response. I understand your concerns and we have those concerns but we don't have a lot of options right now. At least we're talking about one agent that has been demonstrated in a fairly cautious way.

MS. SOLONCHE: Right, but this drug, even if it were not approved is still available to the clinicians who want to use it for their patients. Are we by approving it saying to people this one is better than the other ones rather than what the truth may be, that they were the first. You see my point?

DR. MARGOLIN: Well, for good or for bad we can't legislate the use of the drugs after they are out on the market. All you can do that for is safety so once it was out on the market for Kaposi's sarcoma,

it was available from that time on. This is a vote to recognize that certain criteria have been met that will have to be followed by more rigorous data.

For safety purposes, it's out there and you know that doctors will use it. There's no choice over that and that's true for many. In fact, the use of those other drugs that may be better, may be worse, has come from the same thing. Gemcytabine came out for pancreas and then it started to be used in others. You can't do anything about that.

MS. SOLONCHE: Well, perhaps it's time to look at the statutes and perhaps change that. Not of course at this moment.

DR. DUTCHER: Dr. Simon.

DR. SIMON: I think there is a lot of truth to what you say. I think when drugs are available, it's harder to do clinical trials of those drugs as well as other drugs. I think it was a much better situation with CPT-11 when the company came to us with the randomized trials in second-line colon cancer with essentially palliative treatment control groups in one of the trials and showed the survival

comparison.

I think it's not a good situation to my mind where we approve a drug based on response rate without trials in place or clear indications of what those trials will be to demonstrate whether that drug really does provide any meaningful benefit to women.

DR. SCHILSKY: My only point in bringing up the CPT-11, you know, I think we'll all remember that when that drug first came to the committee the rate of grade III and IV toxicity that was reported at that time was approximately twice the response rate that was reported. Nevertheless, the drug was given accelerated approval. I think most of us probably were skeptical at that point that it would be possible to demonstrate a survival advantage, and yet it turned out that it was possible. So I only bring that up as an example of a situation where a drug with a similar level of activity, albeit in a different disease, ultimately was able to demonstrate a survival advantage in randomized trials.

DR. DUTCHER: Dr. Simon.

DR. SIMON: My only, I guess, issue here

is I would hope that the FDA before giving the drug accelerated approval that they have negotiated clinical trials that they believe will be the basis for approval and what those trials will have to show.

DR. WILLIAMS: Our approval letter generally states such an agreement with specific trial. We generally try to include an advisory committee member in the negotiations.

DR. DUTCHER: Dr. Krook.

DR. KROOK: Simply a comment to my colleague over here. I'll use the same as Rich did with CPT-11. When CPT did 11 and once accelerated approval happened, there was a detail man at my shop fairly quickly and allowed the company to advertise. What I was going to say is the same as Dr. Simon did is that I think we need to set this up.

It also does what you say. It does get in the press. Having been here again for a period of time, it has taken me more than one year to understand accelerated approval. I'm not sure I do yet. It is a different set and it does put the drug out there for people hopefully to reasonably use it.

Those of us in clinical practice like every "business," we know colleagues who don't know how to use drugs and do. As has been mentioned here, we are hopeful that people use it appropriately. I think that's what you're saying, inappropriate use.

The other thing it does by an accelerated approval, it solves some of the reimbursement problems. That did not used to be a problem for me and I suppose not to be talked about here, but it solved some of the reimbursement problems that each of us have to deal with as we go through clinical practice at least for the time being.

As was mentioned earlier by Dr. Williams, I don't think there has ever been a drug that has been withdrawn but that possibility exist in this approval. It's not a full approval so that possibility exist.

DR. SCHILSKY: Jim you know, you bring up an interesting point and I wonder if the FDA has thought about this. That is the ability of practitioners to actually distinguish the differences between accelerated approval and full approval. Whether, in fact, drug companies are required in their

advertising and in their discussions with physicians to indicate whether something has been given accelerated approval or full approval. I think it's a difficult concept. And the fact that it may well be understood in many cases to be that the drug is so good that it was given accelerated approval.

DR. KROOK: Right. That's true. That's true.

DR. SCHILSKY: When, in fact, I think one has to be appropriately skeptical about the value of the drug when it has been given accelerated approval. Maybe you could all comment just to inform us a little bit about what kind of instructions do you give to companies about the parameters that they have to apply in discussing agents after they have been given accelerated approval.

DR. JUSTICE: Well, they can discuss what is on the labeling. One thing that we have been trying to do recently is to make it clear that the approval is based on objective response rate only and the labeling, of course, states the objective response and is not based on demonstration of clinical benefit.

Of course, the company has to advertise according to the approval labeling. That might not get to all the issues but at least it's a start.

DR. OZOLS: One of the things you point out about the other drugs being available is that's what we started with. There are other drugs available. I agree with you that no drug should have the imprimatur that this is the drug of choice out there for second-line treatment because obviously the companies when have FDA approval, it will be something that will come out in marketing.

Having said that, I think it is incumbent on industry and the pharmaceutical industry to get SNDA's out as quick as they can. The agency wants to approve and make sure that the package insert tells where the drug can and can't be used. Drugs like BP-16 and gemcytabine should be coming up here. On the other hand, the agency should make it easier for SNDA's to be done as well, I guess. It's something that in the real world should get out there quicker so that the physicians know that other drugs have activity. In the SNDA's you don't have to worry about

all the toxicity because you've gone over that in detail on your prior submissions. I would like to see a lot more SNDA's out there.

DR. DUTCHER: Excellent discussion. Excellent discussion. I think a lot of food for thought for the negotiations regarding this agent.

We are ahead of schedule so we're going to start ahead of schedule. We're going to start back here at 12:30 p.m.

(Whereupon, the meeting was recessed at 11:17 a.m. to reconvene at 12:30 p.m. this same day.)

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

(12:28 p.m.)

CHAIRPERSON DUTCHER: Good afternoon. We are going to resume the last afternoon of this meeting. We have some new people at the table, so I want to go around once more and just have people briefly introduce themselves. Ms. Beaman?

MS. BEAMAN: Carolyn Beaman, Sisters Breast Cancer Network, Consumer Rep. to the Committee.

DR. SLEDGE: George Sledge, Medical Oncologist, Indiana University.

DR. SANTANA: Victor Santana, Pediatric Oncologist, St. Judes Children's Research Hospital.

DR. NERENSTONE: Stacy Nerenstone, Medical Oncology, Hartford Hospital, Connecticut.

DR. LIPPMAN: Scott Lippman, Medical Oncology, M.D. Anderson Cancer Center.

DR. SCHILSKY: Richard Schilsky, Medical Oncologist, University of Chicago.

MR. GRUETT: I'm Glenn Gruett, Patient Advisor.

DR MARGOLIN: Kim Margolin, Medical

Oncology and Hematology, City of Hope, Los Angeles, California.

CHAIRPERSON DUTCHER: Janice Dutcher, Our Lady of Mercy Cancer Center, New York.

DR. TEMPLETON-SOMERS: Karen Somers, Executive Secretary to the Committee, FDA.

DR KROOK: Jim Krook, Principal Investigator, Duluth CCOP, Duluth.

DR. HARWOOD: Andrew Harwood, Radiation Oncologist with a special interest in head and neck cancer from Louisiana.

DR. SIMON: Richard Simon, Biostatistician, National Cancer Institute.

DR. OZOLS: Bob Ozols, Medical Oncologist, Fox Chase Cancer Center.

DR. WILLIAMS: Grant Williams, Team Leader, FDA.

DR. CHICO: Isagani Chico, Medical Reviewer, FDA.

DR. CHU: Clara Chu, Statistics Reviewer, FDA.

DR. TEMPLE: Bob Justice, Acting Division

Director.

CHAIRPERSON DUTCHER: We have a conflict of interest statement to be read, please?

DR. TEMPLETON-SOMERS: This one is brief. The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the Agency has determined that all reported interest in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting. In the even 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 product they may wish to comment upon. Thanks.

CHAIRPERSON DUTCHER: We have two speakers for the open public hearing. We would like you to please identify yourself, any affiliation with the sponsor, or any financial support. First is Philip J. LoPresti. Please come to the microphone or the podium, either one.

DR. LOPRESTI: Good afternoon, everyone. Madam Chairperson, members of the committee, and representatives of the Food and Drug Administration. I am Philip LoPresti, a retired dermatologist and a survivor of head and neck cancer.

I served my residency at the Hospital University of Pennsylvania, 1963 to 1966, and I taught in the clinic for ten years after, doing various drug studies at the time. I am Chief of Dermatology at Our Lady of Lourdes Hospital in Southern New Jersey, which is a Level 4 hospital, and I was president of the Philadelphia Dermatologic Society, which meets monthly from October to June at the five medical schools in Philadelphia, often presenting rare cases treated with

medications on study programs such as the one I participated in on amifostine.

Therefore, I understand the position you are in today in evaluating amifostine as a possible help for patients with head and neck cancer. I would like to preempt my remarks by stating I am not associated at all with U.S. Bioscience. No one has paid me to appear before the committee today. And as a matter of fact, I drove down to Maryland today from my home in New Jersey in my personal car at my own expense.

I feel I am more familiar than most physicians with patients who suffer from xerostomia, since dermatologists are often consulted for various complications of this disorder such as secondary mammalian infections, bacterial infections, ulcerations and viral infections. However, despite 32 years of practice, I never really appreciated the difficulties from a patient's viewpoint until I became a patient.

My history briefly is I was diagnosed to have squamous cell cancer of the left tonsil. I

underwent a modified radical neck dissection on May 9, 1997. This was done at the Hospital of University of Pennsylvania, and I received my radiation therapy there as well. I volunteered to participate in the amifostine study, and I was fortunate to be enrolled by a random selection pick. I was the first patient placed on the study at the University, and because of the random pick and the fact that patients 2, 3 and 4 were not picked and several patients did not care to volunteer, I was six weeks ahead of the second patient in the study. I bring this out because I feel that no other patient on the drug compared -- I had any reason to compare to, and therefore contribute to placebo effect. However, I could compare my progress with radiation patients that were going through the same treatments that I were, but were not on the amifostine. I received a total of 6300 Gray over a 7-week period.

I would like to share with you my experiences during and after radiation. During radiation, the first thing that happens, of course, is that you lose the ability to taste. I always describe

this as eating wallpaper with the paste on it and no taste. Then as the salivary glands become affected, you can hardly speak above a whisper, and one really dreads the nights. You can only sleep for approximately one hour, and then you must lubricate. And after about the third hour, you are awake and you can't return to sleep. And after three hours of staying awake, you are exhausted. In the early morning, you finally fall asleep and then after sleeping for three hours, you awake with your tongue attached to the roof of your mouth and you are prying your lips from your teeth. The first swallow in the morning is extremely painful. It takes about 45 minutes to eat a bowl of dilute cereal, despite the use of oral demerol. And at that time, I could only eat soups. I lost 35 pounds in 7 weeks and despite high calorie liquid fluid supplements. I had no side effects from the amifostine. No nausea, vomiting, or dizziness.

Now despite all these personal experiences during the therapy, my side effects from radiation, although similar to non-treated patients, were to a

much lesser extent. As I sat in the radiation waiting room, I spoke to many of the patients. I got to know these patients because they were considering going on the study and either were not chose in a random pick or they had questions about the PIC line that I had to have in or the side effects of the drug.

Of course, many of us compared our side effects during our daily meetings in the waiting room. In my discussion with my fellow patients, all had oral ulcerations. I had none. The mucositis I experienced, which I measured by the serous exudate, was markedly less. I was able to eat and speak better than every head and neck patient I spoke with at the center, and some of my fellow patients who did not receive amifostine had to be fed with G-tubes because of their inability to swallow. More importantly, and I think this is the most important point, in addition to the milder side effects I experienced compared to my fellow patients during radiation, the long-term results in my opinion are even more dramatic. And in a patient's viewpoint, rather spectacular.

I am now 22 months post-radiation. I

sleep throughout the night. I eat all foods except for jalapena peppers. One example I would bring to your attention is that for a person with xerostomia to eat bread is like just about impossible. If you try to eat a piece of bread or a bagel, the little saliva you have in your mouth just absorbs it so quickly, even if you take a drink of water it is so difficult to swallow. It doesn't give you the smoothness that saliva does. Well, I can eat bread. I just had a sandwich for lunch with very little help of water to drink.

I recently had breakfast with two patients who were not treated with amifostine. And I invited them to have breakfast with me. I couldn't believe how astonished they were that I could eat a bagel for breakfast and they couldn't even think of ordering that.

Teeth are often carious as a side effect of the pH changes resulting in a high bacteria count. It is recommended the use of fluoride in a mouth p[illegible]ce daily. In July, I elected to have dental braces put on because I was having difficulty with my bite. I

had prophylactic removal of the molars during my surgical bout, and my teeth drifted. While I had braces on, I was not permitted to use fluoride, and this was a period of 7 months. I did not have any caries during that 7 months, or to this day, which is nearly 10 months later. I attribute this to the fact that my rebound of my salivary glands due to the use of amifostine. I consider my speech to be 80 percent of normal. During radiation, I was using salivary topical sprays, a 70 gram Salivart can, 12 cans every 10 days. Now I use 12 cans over an 8-week period.

When I was going through radiation, I was told that 2 months post-radiation I would be much improved, but only to expect 20 percent improvement from there on. I have improved immensely in the past 22 months, and the improvement has been most dramatic in the past 6 months. I do not have to walk through life with a bottle in my hand with limited speech, and I can enjoy the ability to eat all foods. I can sleep through the night.

In conclusion, I would urge the committee to consider this new use of amifostine from the

patient's perspective. I feel I am here on behalf of many patients who cannot speak above a whisper with a terrible quality of life. Surely our goal is to survive. I am grateful that I am in a remission. It is one thing to know that you have a life-threatening cancer, but to compound this with the radiation therapy that will cause tremendous changes in your life via speech, eating, sleeping and tooth decay is staggering to the patient. As we were taught in our early training in medical school, first do no harm. I would urge you to help relieve the patient of these harmful side effects of radiation therapy. Also, I realize one patient's response to therapy does not prove definite efficacy of any medication. Amifostine in my case has cut down on radiation's terrible side effects dramatically. I hope you will not dismiss the improvements in quality of life as trivial. They are important to the patient. I know. I have experienced both ends of the spectrum. I would like to thank you for allowing me to discuss my history before your distinguished committee. I will be happy to provide the committee any first-hand experiences on the course

of treatment should you have any questions about this form of therapy during your deliberations. Thank you.

CHAIRPERSON DUTCHER: Thank you very much. The next speaker is Gail Broder, Cancer Survivorship Alliance of South Florida.

MS. BRODER: Thank you for the opportunity to speak on behalf of patients who can be helped by amifostine. My name is Gail Broder. I am the founder and President Emeritus of the Cancer Survivorship Alliance of South Florida and a six-year cancer survivor. I have no financial interest in the outcome of the ethyol application, and I am here as a volunteer without compensation or reimbursement of expenses.

Among other things, I serve as the patient representative on the Radio and Chemo Protectants Guidelines Development Panel of the American Society of Clinical Oncology, ASCO. Through my participation on the panel, I have become aware of the potential benefit of amifostine for cancer patients receiving radiation treatment to the head and neck. I have not personally been treated in this way and have no first-

hand experience of xerostomia.

Once I became aware of xerostomia as a discrete clinical issue, I realized that I have two friends that suffer from this disorder. Neither of them has ever complained. They accept the problem as a price to be paid for successful cancer treatment. However, it is apparent to me that they experience significant problems with such ordinary activities as eating and speaking.

My friend, Barbara, is 39 years old, and four years ago she was treated for lymphoma, including radiation to the head and neck. She and I spend a lot of time together. She frequently mentions that her mouth is dry, and it is apparent to me that he has difficulty speaking. Even though she continuously drinks water, she seems never to be able to get her mouth sufficiently moist to be comfortable. She has told me that during her treatment the production of saliva all but stopped. I confess, I didn't fully appreciate the effect of her dry mouth problem until she started talking to me about her dental problems. In the months following her treatment, she developed

four cavities. Before that, she had excellent dental health.

My friend, Mort, is in his late 70's. Over 25 years ago, he was twice treated with radiation for head and neck cancer at the University of Pittsburgh. Since then, he too has had difficulty with a dry mouth, and that is over 25 years. He has told me that his mouth is always dry and that he has to continually lubricate it in order to speak comfortable. A humble man, when we eat out, he apologizes for eating so slowly. Because his mouth is dry, it takes him a long time to chew and swallow food. It is difficult for him to carry on a conversation while taking a meal. Mort told me that in the aftermath of his cancer treatment, he required extensive dental treatment.

Since I don't have xerostomia, it would be easy for me to minimize its effect on my friends. It is only because I have spent so much time with both Barbara and Mort that I have come to understand what it means to have this disorder. I now realize that the morbidity associated with xerostomia can be quite

significant for patients with acute and long-term consequences.

The introduction of amifostine into the pharmacy to decrease the incidence and severity of radiation-induced xerostomia is a small, but meaningful advance. As a member of the ASCO Guidelines Development Panel, I reviewed along with the medical experts the available relevant scientific reports and listened carefully to the discussions. I leave it to the medical experts to report the scientific bases for the approval of ethyol. As a cancer patient representative, however, I can say that the panel developed a treatment guideline recommending that amifostine be considered for reduction of incidence and severity of xerostomia in patients receiving radiation treatment for head and neck cancer.

The guideline is based primarily on a large Phase III randomized controlled clinical trial together with numerous Phase I and a randomized Phase II trial. The panel rated the level of this evidence as 2 on a scale of 1 to 5. Based on this level of

evidence, the panel graded the recommendation a B on a scale of A, B, C, D, E and no grade. From a patient's viewpoint, the 2B grade means the evidence is reliable. In making this guideline, the panel found that patients who received amifostine in the randomized clinical trials had significant reductions in incidence and severity of xerostomia. That the drug was generally well tolerated with transient side effects, and that in the randomized clinical trials, there was no evidence in the overall response rates or in overall survival -- there was no difference in the overall response rates or in overall survivor between the group that received amifostine and the one that did not. Importantly, the panel also concluded that there was no evidence from the available clinical data that amifostine leads to the protection of tumor.

I have permission from ASCO to share this information. The guidelines have been formally adopted and will be published I am told in the next few months. I understand that amifostine is continuing to be studied to further substantiate the panels findings, and I encourage the sponsor and its

partners to press on. Thank you.

CHAIRPERSON DUTCHER: Thank you very much. Okay, we are going to then proceed with the sponsors presentation. We have a lot of speakers, so just to warn you, we are putting on a clock. You have your full hour plus 5 minutes.

DR. OSTER: Okay. We tried.

CHAIRPERSON DUTCHER: Okay.

DR. OSTER: Dr. Dutcher, members of the committee, Dr. Justice, representatives from the FDA's Oncology Division and guests, I am Dr. Oster, Executive Vice President at U.S. Bioscience. On behalf of U.S. Bioscience, I want to express our appreciation for having the opportunity to present here today to you the supplemental NDA for the use of amifostine in radiotherapy.

Amifostine is currently approved in the United States to reduce the cumulative renal toxicity associated with repeated administrations of cisplatin in patients with advanced ovarian cancer and non-small cell lung cancer. It is approved for similar or extended indications in approximately 50 other

countries world-wide, including the European community. In the European community, an approval was recently unanimously issued for the use of amifostine in radiotherapy, the indication which we are going to discuss here today.

Post-marketing experience is now available from approximately 250,000 treatment cycles from an estimated 83,000 patients treated world-wide. The emerging safety profile from this observation is consistent with the safety described in the package insert.

The proposed new indication which we present here today is for the use of amifostine to reduce the incidence of moderate to severe radiation-induced xerostomia. This indication has received orphan drug designation by the FDA. According to the FDA's guidance for the industry of standards for the prompt review of efficacy supplements, a priority review can be assigned if the product would be a significant improvement for treatment or prevention of disease.

We submitted this supplemental application

the head and neck cancer but suffer from xerostomia, which they find quite distressing, as you have heard. It really interferes with a patient's daily living.

The data presented for you here today will show that amifostine has demonstrated a clinically meaningful effect on an irreversible morbidity, xerostomia. We show you data from a large, multi-center study using multiple, independent but logically linked endpoints. The findings from this study are statistically persuasive and medically meaningful. Our package also contains a number of supportive studies which we will partly review here, showing the results from efficacy and safety which are consistent with the results from the pivotal study.

I now would like to introduce our scientific team, which has worked together to come to this event today. On the left side, you see the presenters, which are also indicated in your agenda. And on the right side, you see those individuals who have collaborated with us to present to you the data in a scientific and statistical way as they will come to you today. I would like to point out two

individuals who were instrumental in initiating these programs, and these are Dr. Todd Wasserman and Dr. Capizzi. Without these two, we probably couldn't be here.

The next speaker I would like to introduce is Dr. David Grdina, who will present to you data on amifostine's mechanism of action. Dr. Grdina is professor of radiation and cellular oncology at the University of Chicago. Dr. Grdina?

DR. GRDINA: Thank you, Dr. Oster. Amifostine was the premier radioprotector developed by the anti-radiation drug development program that was conducted by the U.S. Army from 1957 to 1973. In this program, DNA was identified as the critical target for protection from radiation-induced damage. Amifostine, by virtue of its positively charged amine groups, can localize and concentrate in the microenvironment of the negatively charged DNA.

However, amifostine is also a pro-drug that must first be dephosphorylated by membrane-bound alkaline phosphatase to its active free thiol and disulfide forms. Now these metabolites are extremely

important because they are very effective in scavaging damage-producing free radicals. Now this is important because 80 percent of the damage by radiation to the DNA is induced through the indirect effect, and that is through the formation of water-based free radicals. So DNA damage by radiation induces free radicals, and it is a very rapid process that is essentially completed within 10^{-3} seconds. Thus, the radioprotector must be present at the time of irradiation. The close association of the active forms of amifostine with DNA allows amifostine to protect against both radiation-induced free radicals and chemotherapeutic drug-generated reactive damaging species.

The magnitude of radial protection is dependant upon the intracellular concentration of amifostine at the time of irradiation. This is best demonstrated by analyzing normal and tumor tissues in a mouse model and contrasting the levels of C-14 labeled metabolites of amifostine that accumulate in them as a function of treatment time. Accumulation varies for normal tissues with salivary gland being

among the most effective in taking up the drug. In contrast, no accumulation above background blood levels is observed in the tumor.

So a number of factors can therefore account for the selective protection of normal tissues. First, deactivation of amifostine is required by membrane-bound alkaline phosphatase, which is highly present in normal vascular endothelium. Secondly, drug delivery to normal tissues is much more efficient by virtue of their more effective functional vasculature as compared to the poor vasculature which is characteristic of solid tumors. Third, this allows for a significant enhancement in concentrations of amifostine to be achieved in normal tissues as compared to tumors. And fourth, since the magnitude of radial protection achieved is dependant upon the intracellular concentration of amifostine at the time of irradiation, the high drug concentrations in normal tissues gives rise to their selective protection.

Finally, in summary, amifostine was designed for and acts as a potent radioprotector. it binds electrostatically to and shields DNA from

radiation-induced free radical damage. With respect to salivary glands, it is highly concentrated in this tissue, and this is accompanied by very high levels of protection to this tissue. And finally, the protective effects of amifostine are concentration-dependent and are selective for normal tissues. At this time, I would like to introduce Dr. Brizel from Duke University and the PI of WR-38, who will speak on the head and neck clinical study with amifostine.

DR. BRIZEL: Dr. Dutcher, members of the advisory committee, Dr. Justice, members of the FDA, and members of the public, I would like to thank you for the opportunity to be here this afternoon to share with you the results of the WR-38 randomized trial of radiation therapy with and without amifostine in head and neck cancer.

I would like to begin by telling you that I am a practicing radiation oncologist, and that the vast majority of my clinical practice is in the care of patients with carcinoma of the head and neck. Radiation therapy, as you have heard, is a primary treatment modality for this group of patients, either

as definitive, curative-intent, stand-alone treatment or as post-operative adjuvant therapy. Depending upon the disease stage and location at the time of presentation, anywhere from 30 to 80 percent of patients who have this disease are potentially curable of their illness.

Necessarily, technical aspects of the delivery of radiation therapy lead to the parotid glands being within the treatment fields. And as we have heard, the parotid glands are very sensitive to the effects of radiation therapy and consequentially, patients do develop xerostomia.

As we have already heard very eloquently from Dr. LoPresti, xerostomia very significantly adversely influences the normal daily lives of patients who have received head and neck radiation therapy. This is the face of xerostomia, and I think we don't even need to be physicians to appreciate that this tongue does not look normal. The mucosa no longer has its glistening moist appearance. We see many cracks and fissures within the tongue.

You have heard from the patient's

standpoint what this means. Let me add my perspective to the picture. And that is, when I examine these patients, it is necessary to use a tongue blade to retract the tongue. And when I am finished and remove the tongue blade, the tongue wants to come with the tongue blade. That is a serious problem in my opinion.

I would like to get a little ahead of myself and take some data from the trial and show you that this is a longstanding problem for these patients. These 64 patients, irrespective of which treatment arm they were in in this trial, had late xerostomia Grade 2, which I will define shortly, at the 12-month interval. Now, of those 64 patients who had late xerostomia 12 months after completing radiotherapy, 63 of the 64 patients still had late xerostomia at the later time point. Once you've got it, you've got it. This is a problem that persists for these patients.

The WR-38 trial had four primary endpoints defined. Number one was the incidence of acute Grade 2 or higher acute xerostomia based on radiation

therapy oncology group guidelines. The incidence of acute Grade 2 or higher late xerostomia was the second endpoint, again as defined by RTOG criteria. Acute Grade 2 mucositis or higher, which is confluent mucositis, was the third endpoint. And finally, the fourth protocol defined primary endpoint of this trial was the preservation of anti-tumor efficacy, which was defined as the local regional control rates at 12 months after the completion of radiotherapy.

Secondary endpoints which were designed to support and reinforce the primary endpoints included the actual time to the development of acute Grade 2 xerostomia, the objective quantification of whole saliva production, patient assessment of their activities of daily living through a repetitive administration of a patient benefit questionnaire, disease-free survival, and finally overall survival.

I think it is worth defining who we are talking about here. The RTOG scale defines Grade 2 xerostomia as moderate to complete dryness of the mouth. So we are looking at this group of patients and worse, and I think it is also worth noting that within

the RTOG scale, there is no Grade 3 xerostomia.

Patients with newly diagnosed squamous cell carcinoma of the head and neck were eligible to be enrolled on this trial, and it was necessary that at least 75 percent of both parotid glands be included within the treatment portals. Also, patients were not allowed to receive prophylactic administration of pilocarpine, also known as salogen.

From October 1995 through October 1997, 315 patients were enrolled in this trial, of whom 303 actually received treatment and they were evenly balanced between the two treatment arms. Through current follow-up, the median follow-up is 26 months, greater than 2 years. Patients were randomized via a dynamic allocation process, but prior to randomization they were stratified according to the following parameters, the first of these being the treatment center, and there were 40 centers that participated and enrolled patients on this trial. They were also stratified by site of disease, presence or absence of nodal disease, Karnofsky performance status, and the type of radiation therapy that they were to receive.

Specifically what that means is either definitive curative-intent treatment, as I mentioned at the outset or post-operative irradiation, where they were further classified as being at either high risk of recurrence or at low risk of recurrence. Again, they were subsequently randomized at that point, either to amifostine plus radiotherapy or radiation therapy alone. Amifostine was given at a dose of 200 mg per m^2 intravenously, 15 to 30 minutes before each fraction of radiotherapy. Radiotherapy was given via conventional once-daily fractionation at 1.8 to 2 Gray per dose, to a total dose of 50 to 70 Gray. The total doses of radiotherapy as well as the technical aspects of the treatment were the same in both treatment arms.

Patient enrollment was well-balanced with respect to age, gender, primary tumor site, T stage, end stage and the type of radiation therapy. On the next two slides, I will go into more depth and detail regarding the balancing of the radiation therapy dose received by the two groups of patients on this trial. Total treatment time is a very important component of the delivery of radiotherapy in clinical care, and we

can see that both groups of patients received their total treatment in the same amount of time. There were no unusual prolongations in the total treatment time. Similarly, we see that the median number of radiotherapy fractions delivered to the two groups of patients was the same.

This is a dose frequency histogram of the radiation therapy which was delivered. And I would like to work with you on this for a brief period of time, because I think that it really demonstrates the equivalence of the dose delivered to the two groups of patients. On the Y axis, we have the percentage of patients receiving a given dose, which would be defined on the X axis. If we go to 90 percent and then work our way across and then down, we see that both groups of patients, 90 percent of them received at least 60 Gray. Let me repeat, in both groups of patients, 90 percent received at least 60 Gray.

Now we see that the median, 50 percent of the patients, the median dose was 64 Gray in the amifostine plus radiation group and 66 Gray in the radiotherapy alone group, and although this median is

higher than this median, that is not a clinically meaningful issue. The real issue is the 60 Gray. Because at a dose of 60 Gray to the parotid gland, we can expect that all other things being equal, xerostomia should probably be complete and long-term. The parotid glands cannot tolerate that sort of dose. And we see that 90 percent of the patients in both groups received at least 60 Gray.

Turning our attention now to the first primary endpoint, acute xerostomia, we see 51 percent of the patients who received amifostine plus radiation reached this endpoint, whereas 78 percent of the patients, a significantly higher proportion of patients who received radiation therapy alone had acute xerostomia. Moreover, what we see is that the dose of radiotherapy that is required to cause this side effect is significantly lower for the patients who received radiation therapy alone. At a dose of 42 Gray, 50 percent of the patients receiving radiation alone already had Grade 3 xerostomia, whereas it was not until a dose of 60 Gray that we saw 50 percent of the patients developing acute xerostomia.

Going back to our frequency histogram, I think we can again see what we are talking about here. At a dose of 40 Gray or 42 Gray rather, 50 percent of the patients with radiation alone are already developing acute xerostomia, whereas it is not until we get to the dose of 60 Gray that we see this same incidence in the patients receiving amifostine plus radiation.

If we try to breakdown the incidence of acute xerostomia by dose of radiation therapy, I think we again take away from this that the vast majority of patients received greater than 60 Gray. And for the smaller group as well, we see that with amifostine plus radiation, there is a lower incidence -- a significantly lower incidence of acute xerostomia than in those patients who received radiation therapy alone.

Moving from acute xerostomia to late xerostomia, we see a couple of things. First of all, as highlighted in yellow, the amifostine plus radiotherapy group had an incidence of 34 percent at one year versus 57 percent for those patients who

received radiation therapy alone, and this is statistically significant. I think it is also fairly clear that our denominator is no longer the 303 patients who were enrolled and who received treatment. We have gotten smaller. And that is a function of the fact that patients do relapse and die of their disease, and so they are not available, many of them, for follow-up at the one-year point.

However, what we did to try to look at this issue in more depth was evaluate late xerostomia at different time points. And once again we see that irrespective of the time point after treatment, we have a lower incidence of late xerostomia in the patients who received amifostine plus radiation therapy than in the patients who received radiation therapy alone.

A more conservative way of addressing this issue, however, would be to go back and include the entire denominator of 303 patients and then see what the incidence of late xerostomia was. And once again, we still see that there is a significant difference in favor of the patients who received amifostine with

their radiation as opposed to those patients who received radiation alone, 22 percent versus 39 percent.

If we try to breakdown late xerostomia by radiotherapy dose, we see the same picture again, just from a slightly different perspective. The vast majority of patients who were alive at this time point received doses greater than 60 Gray, and there was a significantly lower incidence of xerostomia for those patients who received amifostine.

Whole saliva production at one year was a protocol defined endpoint as an independent measure of late xerostomia. And I think the picture becomes clearer here today that the volume of saliva is what ultimately determines patients' symptoms and plays a very important role in their sense of well-being.

The median quantity of saliva that patients could produce at one year if they received amifostine with radiation therapy was 0.26 grams. More than 2.5 times greater than 0.1 gram, the median quantity which was produced by those patients who received radiation therapy alone.

The FDA dental reviewer, based on the pilocarpine precedent, has stated that a quantity of 0.1 grams would be an acceptable indicator of clinical efficacy. Now this was not a prospectively defined protocol endpoint, but it was identified as being clinically meaningful prior to the analysis of any data from the protocol. And with that in mind, we looked at how many patients were able to exceed this clinically significant threshold. The amifostine plus radiation therapy group, 72 percent of the patients exceeded the clinically significant threshold of saliva production, whereas a significantly lower percentage of patients, 49 percent, who received radiation therapy alone were able to exceed this threshold. So a significantly larger proportion of patients treated with amifostine plus radiation therapy were able to produce a clinically significant volume of saliva after their treatment.

It has been proposed that another way to analyze the volume of saliva would be to look at the change from baseline. And I would like to state that I think that this is a potentially complicated way of

looking at the problem. And there are some potential opportunities here to get confused in our conclusions. Because the results, if we are looking at changes from baseline, are driven by the variation in the pretreatment volume. And I will show you some examples in a moment to drive that point, if I may. Furthermore, the change from baseline does not reflect the end of treatment volume. And I don't think it is so important where you start. I think what really matters is where you finish.

Now let's go to our examples. The first patient -- and these are from the WR-38 trial -- the first patient started with 6.5 grams at baseline and finished with just over one gram baseline. Now the change looks fairly dramatic, a negative 5.5 gram reduction. Patient number two started lower at 2.1 grams and finished with nothing at all. The change was -2.1. If we just look at the change from baseline, well this patient has a lower change from baseline, but this is the one who is still making saliva. And I think just looking at change from baseline, we might reach an incorrect conclusion.

I would now like to turn the podium over to Dr. John Mackowiak from the Center for Outcomes Research in Chapel Hill, North Carolina, to discuss with you the patient benefit questionnaire.

DR. MACKOWIAK: Thank you, Dr. Brizel. As a secondary endpoint to corroborate the evidence, the primary efficacy endpoint in this study, a patient benefit questionnaire was included. The questionnaire included eight items, two of which to assess -- I am sorry, three to assess symptoms, three to assess the activities of daily living that were discussed earlier, and two more to assess fluid intake.

The instrument was also validated and I want to share with you the results I reached when I did that validation. One, the instrument has high reliability as assessed by test/retest and also internal consistency. And two, when we do the factor analysis, we found that there was a positive correlation between all eight items. All of them described a single factor. There were not independent factors within that instrument. Therefore, subscales may be helpful to understand what is going on with the

patient, but not absolutely necessary for analysis. The instrument was administered weekly during the time when the clinical benefit was changing most often, and then at months 1, 3, 5, 7, 9 and 11. And in the second year of the study, it was only administered at months 17 and 23 following end of radiation.

These are the mean PVQ scores for the two groups graphed on this graph. What we see is, as was described here, the rapid decline in PVQ scores during radiation, the recovery initially after radiation stopped, and then where you see the persistence of the condition. By looking at the mean scores, you see the separation of the two groups, amifostine and the control group.

At FDA's request and with agreement from the sponsor, a longitudinal analysis was conducted. This was to focus on the multiple comparisons issues as well as to address the issue of non-completers. What I want to do is show you the results of that. The model that was selected also showed that same rapid decline, and then at the end of radiation, the recovery and again the separation. The two lines have

a statistically significant difference as judged by the overall comparison. We also saw statistically significant differences at time points at end of treatment, at end of RT, and also at the end of the follow-up period.

In this graph, what I do is I show you the one-year data and the reason for that as opposed to extending out beyond that. It was the data that was available when the data set was closed in October of last year. Data after that was extremely thin, with only at the 11-month point. And also from what we learned earlier within this clinical trial, the conditions are extremely persistent after that -- extending from the first year onto the second year.

I also wanted to share with you results of one of the other items. This is the general dryness question or the general condition subscale that was presented in the FDA analysis. This is again using the same Laird/Were model, mixed effect model, for that dryness question. We see that same drop during radiation, separation, and then in this case a recovery within the amifostine group. The overall --

there is an overall difference between the two lines, and with this question we do see significant difference at all the time points. All the other items when looked at separately or when collapsed into subscales show a separation. However, the overall significance is not reached. So what we are able to see is directionality within the other items of the subscales, but not a statistical significance when taken one at a time.

This is the same -- the curve lines are the same lines that you saw in the other graph. I superimposed onto that the mean scores taken at each time point. And I show this so you can examine the goodness of fit that is so important when modeling off of mean data. And in this case, the data points do not lie more than a quarter point or a half point away from the curve line. That goodness of fit is a prerequisite to make any statistical conclusions based on that model.

I have shown you a number of -- the PVQ model and this one, and usually the difference or the gap is one point or slightly less than one point. But

I haven't yet said what one point on the PVQ actually means. What is the clinical relevance of that one point? In the next slide, we found consecutive visits within the clinical trial where there was a one grade worsening in the RTOG xerostomia scale. On those exact same consecutive visits, the patients reported approximately a one point decrease in their PVQ score, 0.96, and it was significant. On those consecutive visits when there was one grade level improvement in the RTOG xerostomia scale, the patients reported again approximately a one point improvement in their PVQ. And on those consecutive visits, all the other visits, where there was no change in the RTOG scale, the change in the PVQ score was not significantly different from zero.

With that, I would like to conclude and refer to the fact that as we mentioned before, the PVQ scores we feel are very consistent with the other finding, xerostomia, and based on the data presented here and based on the per-protocol endpoint of mean PVQ score and the analysis plan, we feel that the PVQ does strongly support this application. With that, I

would like to refer back to Dr. Brizel to conclude the efficacy portion.

DR. BRIZEL: Grade 2 xerostomia was the primary endpoint. Saliva production, PVQ scores, those were secondary supportive endpoints. So let us ask the question, how do those correlate with one another? We see -- I really am over 18. For late Grade 2 xerostomia, we see that this correlated in a highly significant fashion with saliva production, PVQ score, and the oral dryness question. Moreover, the PVQ score was highly correlated with saliva production, and reassuring to me as a clinician, oral dryness was highly correlated with saliva production as well.

Now we will turn our attention to the last primary endpoint, preservation of anti-tumor efficacy. As defined in the protocol, the local regional control rates at 12 months were the measure of this endpoint, and we see for amifostine plus radiation therapy, 72 percent local regional control, 71 percent for radiation therapy alone. And we see that the lower limit of the one-sided and two-sided 95 percent

confidence intervals was greater than 0.8. We will hear about this in more depth and detail a little bit later from Dr. Koch.

At 18 months, local regional control 61 percent for amifostine plus radiation therapy, 64 percent for radiation therapy alone. And again, we see the lower limits of the 95 percent confidence intervals around 0.8.

I like to look at pictures better, and maybe that is just because I am a clinician. But if we look at the Kaplan Meier plots, which show what is happening over time for local regional control, we see that there is no difference between the two treatment arms. These are superimposable upon one another. As a radiation oncologist, I would like to digress for a moment and explain why local regional control is so important. Number one, radiation therapy is a local regional form of treatment. So its efficacy is to be evaluated within what is within the treatment field. And secondly, and reinforcing this, is the fact that the vast majority of patients with cancer of the head and neck fail in a local regional fashion for their

initial failure. And we will see that in the next two slides. But here we have the number of failures, local regional failures, and there is no difference between the two groups of patients. So from a local regional standpoint, there is no evidence of compromise of anti-tumor efficacy.

Disease-free survival, which does incorporate non-local failures and deaths from other causes, we again see that the number of events is not different between the two treatment arms. And the two Kaplan Meier plots are superimposable upon one another. So again, with respect to disease-free survival, there is no evidence of compromise of anti-tumor efficacy.

Finally, the ultimate endpoint, survival. Once again, if anything we see more events occurring in the patients who received radiation therapy alone relative to the patients who received amifostine plus radiation therapy. The fact that the amifostine plus radiation curve is above the radiation alone curve is not statistically significant, but once again I really think the important point here is that efficacy has

been preserved. There is not a hint of tumor protection if we look at the survival curves.

For a trial of this type, preservation of anti-tumor efficacy is actually a form of safety. Now the more conventional form of safety that we are used to thinking about is side effects related to the drug itself. As we know, nausea and vomiting are two of the well recognized side effects of amifostine. In this trial, nausea and vomiting was usually mild to moderate in severity, and only 8 percent of the patients had any episodes of grade 3 nausea or vomiting. The really interesting thing to me is this line or this bullet right here. There were over 4,000 administrations of this drug during the course of the trial. Fewer than 1 percent of the infusions of drug were associated with grade 3 nausea or vomiting. 5HT3 antagonists such as zofran were the most commonly used anti-emetics for patients who were on this trial.

Weight loss during treatment is an indirect way of also looking at the nausea and vomiting issue. And if someone were to have persistent, ongoing problems throughout a six-week

course of radiation therapy, one might expect to see a greater level of weight loss in that group of patients. In fact, what we see is that the amifostine plus radiation group of patients lost less weight than the patients who received radiation therapy alone.

Hypotension is the other well-recognized side effect of this drug, and with that awareness, patients received PO or IV hydration 30 minutes prior to the administration of the drug. Overall, 15 percent of the patients had an episode of hypotension. But again, only 1 percent of the infusions were actually associated with any hypotensive episodes. Hypotension, if it was moderate, was only seen in 3 percent of the patients, and this was defined as a drop in systolic pressure greater than 20 mm of mercury. It was transient. There were no long-term sequelae, and once again fewer than 1 percent of the 4,000-plus infusions of the drug were associated with moderate hypotension.

Other grade 3/4 adverse effects which occurred with a frequency greater than 1 percent were skin reactions in three percent of the patients and

febrile reactions in 2 percent of the patients. But once again, fewer than 1 percent of the administrations of the infusions of the drug. And as we would expect, these were not seen in the radiation group.

29 patients did discontinue their amifostine during the course of this protocol, the predominant reason being nausea and vomiting. I would like to emphasize a most important point, however, which is that 28 of those 29 patients did go on and complete their full course of radiation therapy. Again, we need to keep sight of the fact that the objective is to give these patients optimal anti-cancer treatment. So even though 29 patients discontinued amifostine, 28 went on to receive their full cancer treatment.

There were 50 hospitalizations in the amifostine plus radiation group and 31 in the radiation therapy alone group. Of note, however, only six of those hospitalizations were attributable to the drug itself.

To conclude the safety aspects of this