U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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62ND MEETING

TUESDAY,
JUNE 8, 1999

The meeting took place in the Maryland Ballroom, Town Center Hotel, 6727 Colesville Road, Silver Spring, MD at 8:00 a.m., Janice Dutcher, M.D., Chair, presiding.

Present:

Janice Dutcher, M.D., Chair
Karen M. Templeton-Somers, Ph.D., Executive Secretary
James E. Krook, M.D., Member
Kim A. Margolin, M.D., Member
Stacy R. Nerenstone, M.D., Member
Robert Ozols, M.D., Ph.D., Member
Victor M. Santana, M.D., Member
Richard L. Schilsky, M.D., Member
Richard M. Simon, D.Sc., Member
George W. Sledge, Jr., M.D., Member
E. Carolyn Beaman, M.H.S., Consumer Representative
Martha Solonche, Patient Representative
Glenn Gruett, Patient Representative
Andrew Harwood, M.D., Consultant
Scott Lippman, M.D., Consultant
Isagani Chico, M.D., FDA Representative

Present: (cont.)

Clara Chu Ph.D., FDA Representative
Gregory Frykman, M.D., FDA Representative
Robert Justice, M.D., FDA Representative
Grant Williams, M.D., FDA Representative

Public Comment:

Gail Hayward (letter)
Susie Bendel
Philip J. LoPresti
Gail S. Broder

Edward Schnipper, M.D., Sponsor Representative
Maurie Markman, M.D., Sponsor Representative
Frank Martin, Ph.D., Sponsor Representative
Ken Cunningham, M.D., Sponsor Representative
Wolfgang Oster, M.D., Sponsor Representative
David Grdina, Ph.D., Sponsor Representative
David Brizel, M.D., Sponsor Representative
John Mackowiak, Ph.D., Sponsor Representative
Gary Koch, Ph.D., Sponsor Representative
Lesley Russell, M.D., Sponsor Representative
Walter Curran, M.D., Sponsor Representative
Randy Allred, Dr.PH., Sponsor Representative
Alan Gordon, M.D., Sponsor Representative
William McGuire, M.D., Sponsor Representative
Franco Muggia, M.D., Sponsor Representative
Todd Wasserman, M.D., Sponsor Representative

Also Present:

Gang Chen, Ph.D.

A-G-E-N-D-A

A-G-E-N-D-A

NDA 20-221/S-012, Ethyol (amifostine) for injection
U.S. Bioscience, Inc.

Sponsor Presentations

A-G-E-N-D-A

NDA 20-221/S-012, Ethyol (amifostine) for injection
U.S. Bioscience, Inc. (cont.)

FDA Presentation

P-R-O-C-E-E-D-I-N-G-S

(8:02 a.m.)

DR. DUTCHER: All right. We're going to get started. This is day two of the 62nd Oncologic Drug Advisory Committee. Welcome. Today we are going to be discussing two agents. One is Doxil and one is Ethyol. Before we get started I would like to go around the table and introduce people who are sitting at the table.

Ms. Beaman.

MS. BEAMAN: Good morning. I'm Carolyn Beaman, Sisters Breast Cancer Network, consumer rep. to the committee.

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

DR. SANTANA: Victor Santana, St. Jude's Childrens Research Hospital, Pediatric Oncologist.

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

MS. SOLONCHE: Martha Solonche, SHARE, New York City, Patient Rep.

DR. SCHILSKY: Richard Schilsky, Medical

Oncologist, University of Chicago.

DR. MARGOLIN: Kim Margolin, Medical Oncology and Hematology, City of Hope, Los Angeles, California.

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

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

DR. KROOK: Jim Krook, Medical Oncologist, Duluth, Minnesota.

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

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

DR. FRYKMAN: Gregory Frykman, FDA Reviewer.

DR. JUSTICE: Bob Justice, Acting Division Director.

DR. DUTCHER: Thank you. We are now going to read a conflict of interest statement.

DR. TEMPLETON-SOMERS: 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 with the following exceptions.

In accordance with 18 U.S.C. 208(b) full wavers have been granted to Drs. Kim Margolin and Victor Santana. Copies of these waver statements may be obtained by submitting a written request to FDA's Freedom of Information Office located in room 12A-30 of the Parklawn Building.

In addition, we would like to disclose for the record that Drs. Richard Schilsky and Robert Ozols have interest which do not constitute financial interest within the meaning of 18 U.S.C. 208(a) but which could create the appearance of a conflict. The agency has determined notwithstanding these interests

that the interest of the Government and their participation outweighs the concern that the integrity of the agency programs and operations may be questioned.

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

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

DR. DUTCHER: Thank you. The open public hearing today is going to be in two parts. We are going to read a letter now and then after the presentations we are going to have a speaker.

The letter is from Gail Hayward, an ovarian cancer survivor, and president and founder of the National Ovarian Cancer Coalition.

DR. TEMPLETON-SOMERS: "I wear two hats when I enter the ovarian cancer world. One hat is that of president and founder of the National Ovarian Cancer Coalition, NOCC. The second is that of ovarian cancer survivor since 1989. I have fought to survive nine and one half years without a remission of the disease.

Ovarian cancer is life threatening. More than 50 percent of the women who have it die within five years of diagnosis. That is because in at least 70 percent of cases women are not diagnosed until the cancer has reached an advanced stage when it is often too late to cure.

In these all too common cases the fatality rate is an alarming 80 percent. For those of us who live longer, our lives are often a roller coaster of tough chemotherapy treatments, numerous side effects, and a continuing anxiety-filled search for what to do next when the current protocol is no longer effective.

For me the suffering has brought with it not only physical decline but, even more difficult, post-traumatic stress along with stressful financial

difficulties. The far-reaching tentacles of ovarian cancer deeply affect our family members.

Despite the continuous onslaught I have developed an insatiable desire to live. My daughter died of cancer a year ago. She left two little boys now age 8 and 9. I have made a decision that I will be there for them as they grow. They need me and I need them. I am deeply grateful for every breath I take.

I founded the NOCC in 1993. In 1996 we got our not-for-profit status. The organization started out with a group of 20 women in a support group. We now have over 11,000 members, 20 state chapters, and we reach literally millions of people each year with awareness and educational programs for ovarian cancer.

Busy? You bet. But the organization is a gift to me. It is not an accomplishment that can be done by one. Dedicated people have come forward and offered their undaunting support of time and effort to dispel myths and misunderstandings about ovarian cancer and they have committed to improve the overall

survival and quality of life from ovarian cancer. NOCC collects the personal letters sent to us by thousands of ovarian cancer survivors and their families. Above all they want hope.

Like myself many have been through paclitaxel- and platinum-based chemotherapy regimens as well as topotecan. Doxil, doxorubicin hydrochloride liposome injection, is an innovative drug in a new wrapping that delivers the drug effectively and without the horrendous side effects usually experienced by most chemotherapies. It gives hope for extension of life with quality of life. I have personally met with representatives from ALZA and was educated about Doxil.

I nor NOCC has any financial obligations to this pharmaceutical company. I am convinced, however, through my own personal experience of taking Doxil for 10 months along with my knowledge of the drug that Doxil should be made available to women like myself who are refractory to many other agents.

I speak not only for myself but also for the 185,000 women alive with ovarian cancer today.

Gail Hayward, ovarian cancer survivor and president and founder of the National Ovarian Cancer Coalition."

DR. DUTCHER: Thank you. We are now going to proceed with the sponsor presentation. I should forewarn you that we are going to be using a timer today because we have so many speakers. You do have an hour to complete the presentation and then we'll have questions for the sponsor.

DR. SCHNIPPER: Good morning. On behalf of ALZA Corporation I am Ed Schnipper and I would like to introduce our program this morning. Doxil is currently approved for use in patients with AIDS-related Kaposi's sarcoma who have relapsed on chemotherapy or who are intolerant to chemotherapy.

We are here today to present our supplemental NDA for use of Doxil in patients with advanced refractory ovarian carcinoma. Specially, we are asking for an indication for patients with metastatic carcinoma of the ovary who are refractory to both paclitaxel- and platinum-based chemotherapy regimens and who also may be refractory to topotecan. Refractory in this setting is defined as a patient who

has progressed the disease while on therapy or within six months of therapy.

The agenda for this morning will begin with a talk from Dr. Maurie Markman on the unmet medical need followed by Frank Martin who will speak about the technology behind Doxil and some of its pharmacology. I will then speak about the efficacy studies that are in the SNDA, followed by Ken Cunningham who will speak about the safety of Doxil. I will return to make some concluding remarks and will be happy to take any questions you might have.

Also with us today are several consultants that will help us answer any questions. All of these consultants have been participants in our clinical trials. We have with us today Dr. Alan Gordon of the Sammons Cancer Center in Dallas, Dr. William McGuire of the University of Mississippi, and Dr. Franco Muggia of NYU Medical Center.

In addition, I have with me several of my colleagues from ALZA who will again help me answer any questions that you might have. I would now like to introduce Dr. Maurie Markman from the Cleveland

Clinic.

DR. MARKMAN: Good morning. It is a pleasure to speak to you briefly this morning on the topic of the unmet medical needs regarding ovarian cancer. In hearing the letter from Ms. Hayward, I must acknowledge that it is impossible for me to say more than she said in her letter. It was obviously truly profound statements.

Ovarian cancer affects approximately 25,000 women in the United States each year. Unfortunately, there will also be approximately 14,000 deaths associated with this cancer.

As you have so eloquently heard, the fundamental problem is it is currently extremely difficult to find the disease in its early stages. In fact, 70 percent plus of women with this malignancy will present with advanced disease where the standard treatments currently are the platinum agent and paclitaxel.

Despite what I certainly would characterize as substantial improvements in the chemotherapy for this malignancy both from the

perspective of response rate and survival and, importantly, quality of life, the bottom line is more than 20 percent of women with this malignancy receiving chemotherapy will fail to respond to front line treatment.

In the advance disease, particularly suboptimal disease setting, 80 percent of patients will ultimately relapse and be candidates for a second-line treatment approach and just from the perspective of definitions to some that you are going to hear in the next few moments.

It has been learned through experience in not only ovarian cancer but other malignancies as well that it is important when you talk about second-line therapy to divide your patient populations up into two relatively broad categories that have very important clinical meanings regarding treatment options.

The first is so-called sensitive patient population. That is a population that has a very realistic chance of responding to retreatment with the same or similar drug that you have just given them. For definitional purposes we will define those

individuals who have had a response to therapy and they have been off therapy for at least six months, and that is the population which we are not going to discuss further, certainly because we actually have relatively reasonable treatment options available today in that setting.

But it is the refractory patient population, those who have progressed while on therapy or never responded to therapy, or progressed within six months of the completion of therapy who are very unlikely to respond to retreatment with the agents they received. That is going to be the focus of our attention and the truly unmet needs.

There are actually three drugs that I can mention that are currently approved as second-line treatment of ovarian cancer, paclitaxel, altretamine, and topotecan and just very briefly to show you some of the response rates. The purpose of my presentation is certainly not to do any comparisons or contrasting or anything of the sort, but just to give you an idea of the kind of objective response rates that have been reported and confirmed in the medical literature.

The patient populations vary certainly. This is somewhat of a moving target based on what the current front line therapy is because that becomes then the standard to which you want to compare your second-line treatment strategies to because those are the drugs that the patients will have failed and that's what you are then going to use.

If you look at topotecan there is data of about a nine to 10 percent response rate in paclitaxel patients. In those individuals who have received platinum and topotecan, the response rate of paclitaxel is about three percent. Actually, with altretamine, which is an older drug and, therefore, was not really tested in that era of the platinum paclitaxel topotecans, we really do not know what the objective response rate.

And to that population that is resistant to platinum, paclitaxel, and topotecan, which is now a relatively common population as these three drugs are widely used, we actually have no objective data, certainly not presented to ODAC, to demonstrate what the anticipated activity is of any drug in this

setting.

Now, very briefly there are several factors that are known to very much influence the chances of a second-line agent working in a refractory setting. Certainly the worse population from the perspective of coming up with an agent that has activity that's going to have meaning for patients is that patient who is truly progressed on initial platinum-based chemotherapy. Again, in 1999 that's platinum and paclitaxel.

And, of course, a patient who has progressed after multiple regimens, clearly that tumor has demonstrated to have developed a variety of resistance mechanisms and, therefore, the chances that the next drug you're going to try is going to work is, of course, increasingly small.

However, it is important to point out that ovarian cancer is different than many other malignancies and, therefore, this question of second-line or third-line or fourth-line therapy, whatever you want to call it, is a very meaningful question in this malignancy where it may not be in another

malignancy.

Again, Ms. Hayward's comments, her long survival, her multiple chemotherapeutic regimens is a very poignant example of the reality of treatment of ovarian cancer in 1999.

Relapse is common as I suggested. However, prolonged survival is also common and becoming increasingly common. In fact, most recent projects based upon follow-up on trials in women with advanced ovarian cancer treated with platinum paclitaxel based regimens advanced disease but so-called optimal residual disease.

In other words, stage-three disease with a relatively small amount of cancer remaining in the abdominal cavity, 40 percent of that population will be alive 10 years after diagnosis. Long survival is becoming increasingly what we would anticipate. However, again, the relapses are common.

And importantly, particularly when we talk about the issue of is it appropriate to even consider second-line therapy, this patient population very fortunately often has an excellent performance status

for a very prolonged period of time and, therefore, they are reasonable candidates to at least consider a second-line treatment option. In other words, it is important to have those options available for the patients to think about.

In addition, it is important to point out that even though we do have other agents that have been approved for second-line therapy in the management of ovarian cancer, it is important to argue very strenuously that we need to have options, not just one drug. The reason for that is very simple.

Based upon the individual patient characteristics and their prior response and, importantly, prior toxicity to the front line therapy, the choice of a second-line regimen may very well be influenced by those factors. I just give three very simple examples that all the oncologists on the panel are very aware of.

An individual who has received prior front line therapy, the platinum paclitaxel, may very have experienced neurotoxicity from the front line regimen and, therefore, that's an individual if you had

options available in the second-line setting you would certainly want to stay away from drugs that had neurotoxicity as a potential effect.

An individual who had excessive bone marrow toxicity with the front line regimen, very much you would want to try to stay away from a regimen that you knew had major toxicity as bone marrow toxicity. Of course, the obvious problem of somebody with a lot of nausea and vomiting you very much want to stay away from an agent that you knew had a potential toxicity to be significant nausea and vomiting.

Finally, because this patient population is able to live for so long with overall such good quality of life, it is critical as we think about second-line, third-line agents that we think about those agents that are well tolerated and convenient for patients.

The last thing we want to do is take a patient who is doing well but still has active disease and make the quality of life bad. Clearly all of these agents have toxicities. They are cytotoxic, the ones we are talking about. They have the potential of

causing harm but we have to do our best to cause the least possible harm so that we can prolong survival and hopefully improve the quality of life. I thank you for your attention.

DR. MARTIN: Good morning. My name is Frank Martin. I'm principal scientist at ALZA Corporation. The key structural feature of all liposomes including the Doxil liposome you'll hear about today is a lipid biolator membrane made out of material such as phosolipids and cholesterol.

These membranes when they are exposed to water, or these lipids when they are exposed to water, spontaneously form membranes that wrap around a small portion of the aqueous compartment forming a structure that is much like a small cell, a tiny cell.

In the case of Doxil there is a single such lipid biolator membrane and the overall dimensions of the particle is about 100 nanometers. So to give you a point of reference, this is about 1/100th the size of a red blood cell. These are small particles.

There are two structural features that

differential Doxil from other liposomes. The first one is the way the drug is loaded. Doxorubicin hydrochloride is actively pumped into the internal compartment of these liposomes using an ion gradient method. It's possible to achieve such high concentrations of doxorubicin internally that the drug actually falls out of solution forming a gel like precipitate inside the liposome.

This is important because it leads to very stable encapsulation of the drug and to a very high amount of drug in each liposome. Indeed, it is possible to load about 15,000 molecules of doxorubicin in a single liposome of this size.

It also leads to very robust stability because these particles, as you will see in a moment, to do their job are going to have to circulate in the bloodstream for days so we want to keep the drug in the liposome in order to optimize the amount that's delivered to the target site.

The other feature is the hallmark of a STEALTH liposome, and that is the polymer layer which is chemically grafted to the surface of the liposome.

The polymer is polyethylene glycol, which is known to be an inert safe polymer, and it forms a very dense hydrophilic layer around the liposome.

This layer is designed to do two things; to keep biological proteins and plasma from binding to the liposome and destabilizing it, No. 1, and, No. 2, to reduce the rate at which the reticuloendothelial system recognizes and clears these particles from the bloodstream. It's intended to make like a tiny formed element in blood.

Now, by virtue of the way the drug is encapsulated, the small size, and the polymer coating, these liposomes circulate for long periods of time after intravenous administration. This is illustrated here with the pharmacogenetics of Doxil in cancer patients showing on this axis the concentration of doxorubicin and plasma over a seven day period after administration.

There are two curves plotted here. One is the total amount of drug in the bloodstream over this period. The other is the proportion of that total that is still liposomes. I would like to draw your

attention to two important points here. The first is virtually all of the drug remains in the particles while they are circulating in the bloodstream. The other is the clearance is very slow.

Indeed, the half-life for Doxil is about two to three days in these cancer patients. By virtue now of their small size and long circulation time, these particles are able to access sites of disease that have abnormal blood vessels. In one such site is tumors.

It is well known now that tumors have defective capillaries particularly in areas undergoing angiogenesis where these capillaries are sprouting. They are growing so haphazardly and so quickly that defects and gaps are present in the endothelial walls. These liposomes are small enough to physically extravasate through these gaps and lodge in the interstitium of tumors.

Evidence for that is shown here in a preclinical model. This is a xenograft of a prostate cancer in mice. In this study what we are doing is looking at the area under the curve in the tumor after

a single dose of either Adriamycin or Doxil at time zero. You can see that the pattern of uptake is quite different for these two drugs.

In the case of Adriamycin, the uptake is rather rapid and the elimination rate is rather fast. This is in full agreement with what one would expect from the literature. The Adriamycin enters the tumor and is cleared within a few hours.

An identical doze of Doxil has a different pattern. First of all, it takes several days to reach its peak. The peak is higher meaning that these liposomes are actually carrying more drug to the tumor. The residence time in the tumor is very long taking a week in this rodent model for the drug to be eliminated.

Our interpretation of these data are that, No. 1, it takes a long time for the liposomes to enter and they enter as intact particles. That is, the drug is still in the particle. Then over the ensuing time period the liposomes break open, release their drug, the drug becomes bioavailable, is metabolized and eliminated from the tumor.

This differential uptake pattern is also seen in humans. In the next slide what I'm going to be showing you is a gamma scintigram of a patient, a completely sarcoma, where we injected not Doxil but the same liposomes containing Indium 111, Indium 111 chelated to EDTA so that we can use gamma scintigraphy to follow both the kinetics and the distribution of the liposomes.

Importantly this method only tracks or reports the presence of intact liposomes. If the chelate is released from the liposome, it is immediately eliminated in the urine within just a few minutes. The radioactivity is reporting the existence and movement of intact particles.

Shown in the first panel is the gamma scintigram at four hours post injection. I'm drawing your attention here to this patient's left where there are several Kaposi's sarcoma lesions. The lesion I would ask you to follow is the lesion that is circled.

At four hours you can see clearly that the major radioactive distribution is blood pool. That is, the major vessels in the chest are shown. You can

see some activity in the bladder which represents the Indium EDTA that was not in the liposomes when they were injected so this was immediately eliminated in the bladder.

You could start to see uptake in the lesion at 24 hours. It reaches a maximum uptake at 48 hours. Yet, even at 96 hours all of these lesions in the leg are positive indicating two things. (1) it takes a while for these lipsomes to get into the lesion, and (2) even at 96, and we even have other time points later at two, three, or four days later the liposomes remain in the lesion as intact particles so they are lingering in the lesion for some period of time.

The uptake pattern in Kaposi's sarcoma has been verified biochemically as shown here in a group of seven KS patients who were injected with Doxil at time zero and 48 hours later a representative cutaneous lesion was biopsies as was adjacent normal skin beyond the margir of the lesion. The total drug in these tissues was then measured and you can clearly see that the amount of drug in the lesion is much

higher than the amount of drug in adjacent normal skin in all of these patients.

Differential uptake in Kaposi's sarcoma seen here does provide benefit to Kaposi's sarcoma patients. Indeed, Doxil was first approved for use in patients with Kaposi's sarcoma that had failed first-line therapy and including a group of patients that had received prior Adriamycin. Response rates in the original submission are shown here.

Since that time randomized trials have been conducted of Doxil as a single agent versus a variety of combinations including ABB, BV, and the Doxil plus BV. In all of these trials a high response rate in Kaposi's sarcoma has been confirmed and these are all now in the medical literature.

Of course, we were interested in other histologies beyond Kaposi's sarcoma. Adriamycin is active in a variety of solid tumors so preclinically we screened a variety of tumor types in xenograft and rodent models. One model we tested was an ovarian cancer xenograft, the HEY xenograft. Indeed, we found activity of Doxil in the xenograft as shown here which

is a typical tumor growth curve.

Here is both sides of the tumor versus time after implantation. As you can clearly see, Adriamycin is active in this model versus the control group. Doxil at the same administered dose as superior activity to Adriamycin.

Based on the preclinical activity that we saw here and based on some work done in a Phase I trial in which a group of heavily pretreated ovarian cancer patients was admitted into a Phase I trial and work done by Franco Muggia, we found clinical activity in a number of these patients including a bona fide partial responder and some miner responses.

Based on the preclinical activity of Doxil in ovarian cancer and indication of clinical activity really represents the rationale for our looking into the utility of Doxil in ovarian cancer which will be the topic of discussion today.

I would like to ask Dr. Schnipper to return and to begin the sponsor's clinical presentation.

DR. SCHNIPPER: The clinical development

of Doxil for ovarian cancer began in 1994 and was designated an orphan designation in 1998. The supplemental NDA that we're talking about today was filed in December of this past year and granted priority review earlier this year.

The data that I'm going to discuss today will demonstrate that Doxil is active in these refractory patients, the Doxil is generally well tolerated, and the Doxil is convenient to administer.

The program consist of four trials, three noncomparative trials and preliminary results from an interim analysis of a randomized Phase III comparative trial comparing Doxil to topotecan.

The three multicenter noncomparative trials all contained relapsed or refractory patients. Refractory, as we said, is narrowly defined as patients who have progressed while receiving therapy or within six months of receiving therapy, patients who are defined as platinum and paclitaxel refractory, to fill that definition for both drugs whether they were given individually or in combination.

Similarly, patients who were additionally

refractory topotecan also fill that definition for all three drugs either individually or if the drugs were given in combination.

The primary endpoints of all these studies were response rate and all responses were based solely on measurable disease. All responses were confirmed by repeat radiologic scan at least four weeks from the demonstration of response. All available scans were subjected to independent radiologic review. Secondary endpoints included time for regression and duration of response.

The initial dosing regimen for all three files with the exception of trial 30-22 was 50 milligrams per meter squared every four weeks. The median dose actually received across all three trials was 50 milligrams per meter squared every four weeks.

The Phase II trials were conducted at multiple sites. Two of the studies were done in the U.S. and one in Europe. The median age is shown here. The number of patients in each trial that fulfilled a definition of being refractory to platinum and paclitaxel was 28, 49, and 26 respectively.

In Study 30-47 there were 33 patients that additionally fulfilled the criteria for being refractory to topotecan and 10 patients in Study 47E.

It is also important to note that there was quite a short interval between patients having received their prior regimen and progressive disease before entering on the Doxil trials. In addition, most patients had received two more prior regimens.

I would like to now turn to the results of these three trials. Of the 28 patients in Study 30-22 who fulfilled the definition for being refractory to both paclitaxel and platinum. There were six responders. One complete and five partial responders for an overall response rate of 21.4 percent.

In 30-47 there were 49 patients who fulfilled that refractory definition. There were nine partial responders for a response rate of 18.4 percent.

If you look at the patients that also fulfilled the definition of being refractory to topotecan, there were 33 patients, six responders, one complete, five partial for a response rate of 18.2

percent. In Study 47E there were no responses in the patients who fulfilled the definition for refractory.

Now, we looked at a variety of factors to explain why the results from 30 and 47E were not consistent with the results from the other two trials. In looking at some of these factors, we noted that there were indeed a couple of differences between the patients in this trial and the patients in the other trials.

For example, the baseline CA 125 was somewhat larger. The bulky disease, the sum total of measured disease at baseline was somewhat larger. Patients spent a shorter amount of time on trial. Patients who left trial in general left trial for death or progressive disease rather than toxicity.

So it appears that it is at least possible that the patients on this trial entered at a later stage in their disease and were treated perhaps for shorter periods of time than the patients in the other trials thus making it more difficult for them to respond. Nonetheless, these patients are included in our overall analysis of response rate.

Looking at all the responses together across the trials we can see that for the platinum and paclitaxel refractory patients, it was an overall response rate of 14.6 percent. If we look at those patients that were additionally refractory topotecan, the response rate was 14.0 percent. Combining all the patients together, the response rate was 14.4 percent.

As Dr. Markman stated, some of the most difficult patients to treat are those who actually progress while on platinum. If you look at just those patients, the response rate was 10 percent in those extremely difficult to treat patients.

A Kaplan Meier curve of duration of response showed a median duration of response of 39.4 weeks, almost 10 months. The time to progression across all these trials was 15.9 weeks, almost four months.

If we also look at performance status of these patients and plot a Kaplan Meier curve of first decline and performance status and put that on the same curve, same chart as the time to progression, we can see the two curves are parallel. Patients

maintain their Karnofsky status until the time of progression. Patients were generally were able to continue their daily life while on therapy.

If we turn our attention now to our randomized trial, Study 30-49, this was a study designed for patients who had failed primary therapy with platinum. The patients were then randomized to receive either Doxil, 50 milligrams meter squared every four weeks, or topotecan, 1.5 milligrams per meter squared daily times five every three weeks.

Patients were required to have measurable disease. In this study the primary endpoint was timed to progression with endpoints response rate, duration of response, etcetera, also looked at.

The study was conducted at 90 sites throughout the United States and Europe and has recently reached its target accrual of 460 patients who have continued to be followed for response.

What we are showing here is the results of the first planned interim analysis that per protocol was scheduled to be undertaken when 200 evaluable patients were entered. We are going to talk only

about the 237 intent-to-treat patients that were accrued to reach this goal.

Those patients would have had to have at least six months of follow-up to be included in this analysis. We will present the entire population for safety and we will concern ourselves for efficacy with that subset of patients, 81 patients, that met the definition that we have said before, for being refractory to platinum and paclitaxel.

Of the 44 patients on the Doxil arm who met that definition, there were six responders for a response rate of 13.6 percent, pretty much in line with what we've seen from the Phase II trials. On the topotecan arm, there were 37 patients, three responders for a response rate of 8.1 percent.

We've talked a lot about response rates. What about the magnitude of these responses? What we have here is a graphic representation of a table that you all have in your briefing documents that looks at all the patients from all the studies, a total of 27 responders, and looks at the percent reduction in lesions. As you can see, the majority of the patients

had quite large reductions in their lesions from baseline to when it was measured as a responder.

In fact, nine patients had complete disappearance of all measurable disease. Only two of them were considered complete responders because under the strict definition of complete response, some of these patients may have had an ill defined shadow on CAT scan or some unevaluable disease so they were not considered complete responders but, in fact, had disappearance of all measurable disease.

As you can see, there were very few patients that, in fact, qualified as responders by having only relatively small differences from baseline in their measurement of disease.

I would like to just briefly summarize the Phase II efficacy data that we've discussed by saying that across all studies we had a response rate of 14.4 percent in these highly refractory patients. The duration of response was almost 10 months with a time to progression of almost four months thereby demonstrating activity of Doxil in these highly refractory patients.

I would now like to introduce Dr. Ken Cunningham to talk a little bit about the safety of Doxil.

DR. CUNNINGHAM: Good morning. My name is Ken Cunningham. I would like to present to you the safety profile of Doxil. The experience comes from five ovarian studies totally 408 patients. It is this population which I intend focusing on this morning. We have a further 772 patients in the total solid tumor population, and in the Kaposi's sarcoma clinical experience we have 1,721 patients. This additional experience is consistent with the ovarian experience.

Turning first to drug exposure, the median cycle dose was 50 milligrams per meter squared. The median cycle length, 29.5 days. The cumulative dose was approximately 150 milligrams per meter squared, some patients receiving a lot more.

This graph shows the dosing tensity by cycle. Now, some 42 percent of patients actually dose modified. That is, they had a dose reduction or a dose delay. But you can see that a high dosing tensity was sustained throughout. Indeed, at the 6th

cycle 11.2 milligrams per meter squared was the mean dosing tensity which is 90 percent of the intended.

Turning to adverse events, you can see that from this chart that the patients who experienced adverse events, the majority had grade I or grade II, 60 percent had grade III, and a substantially fewer number had grade IV. There were four deaths on study. One of these deaths was considered to be drug related and that was a patient with neutropenic sepsis who had been heavily pretreated.

I should point out that the numbers on this chart are 396. That's the total number of patients on whom we received adverse event report forms.

Palmar-plantar erythrodysthesia, or PPE, sometimes known as hand-foot syndrome is the commonest side effect with Doxil. You can see that the majority of patients have mild to moderate events but some 17 percent have grade III. Two patients in the ovarian population were categorized as having grade IV.

Stomatitis is the second commonest. but, again, the majority of patients have mild to moderate

events. You can see a similar pattern as we move down the other adverse events, the majority mild to moderate events.

Alopecia occurred in 16 percent of patients. This was mainly minor hair thinning although .7 percent of patients had some more extensive hair loss.

Looking at the hematologic laboratory data and focusing on the severe grade III/grade IV events, neutropenia occurred at grade IV in 8.6 percent of patients. That is, a neutrophil count of less than 500. Relatively few patients had growth factor, 4.1 percent. Only one patient was reported as having neutropenic sepsis.

Slightly more patients had anemia. 16.4 percent had grade IV anemia with hemoglobin of less than 6.5 grams. Consistent with this figure, 14 percent had blood transfusions.

Thrombocytopenia was less frequent. 1.2 percent of patients had a platelet count of less than 25,000 and very few patients had platelet transfusions.

Eleven percent of patients withdrew due to adverse events and the commonest reason was Palmar-plantar erythrodysthesia, 3.5 percent. The other events can be seen here and all account for 1 percent or less of withdrawals.

I would like to say a few words on the management of PPE. Looking first the grading system, PPE affects the palms of the hands, the soles of the feet. In its mildest form is erythema that the patient may not even be aware of. Sometimes it's associated with tingling.

As we move through to grade II there is erythema in association with sometimes edema and sometimes desquamation. Grade III, some blistering. grade IV is obviously a more diffuse problem.

With grade I we suggest redosing. Obviously there are other recommendations to the patients. The patients are advised to wear loose fitting clothing, they shouldn't wear shoes which are too tight, or indulge in any activities which would tend to rub or abrade the skin.

At grade II a delay of one to two weeks

should be instituted. At grade III and IV a similar delay but this time when the patient is redosed they should be redosed at 75 percent of the original dose.

We propose that we put this in our PI. We also believe that with good education and following this plan we can minimize the effect of PPE.

When considering an anthracycline, clearly cardiac toxicity should be considered. In our total solid tumor database of 772 patients -- we're now talking beyond the ovarian population -- we had six patients who withdrew due to cardiac toxicity. Five had asymptomatic left ventricular ejection fraction declines. One patient had congestive heart failure. That patient had, in fact, had 22 cycles and a cumulative dose of 944 milligrams per meter squared.

Five additional drug related cardiac events were reported, all grade I. Doxil pharmacokinetics mimics the pharmacokinetics of continuous infusion doxorubicin and it has been well established that continuous infusion doxorubicin is associated with less cardiac toxicity.

We've also done some animal work,

preclinical animal models including the rabbit have been studied and shown that milligram for milligram doxorubicin causes more cardiac toxicity than Doxil.

A limited amount of biopsy data has been performed. As you are aware, biopsy data is probably the most sensitive way of looking at anthracycline and toxicity.

In one study with 10 KS patients, patients received between 469 and 860 milligrams cumulative dose of Doxil. They showed minimal cardiac toxicity based on the Billingham score. A Billingham score of 1 is the first point on the three point scale that indicates or denotes cardiac toxicity.

We've also looked at four solid tumor patients and their doses range from 675 right up to 1,680 milligrams. In two cases these patients had prior Adriamycin of at least 300 milligrams. You can see again that the Billingham score runs from nought to 1.5 so minimal cardiac toxicity, although far more data is needed to generate sufficient information on this subject.

As Dr. Schnipper has already mentioned, we

are currently conducting a large randomized comparative study in ovarian cancer, Doxil versus topotecan.

So far in this study we have recruited 135 Doxil patients and 132 topotecan patients. This interim safety analysis has about four months of safety update reviews to the FDA.

You can see from this that between 40 and 45 percent of patients are still on study. Terminations are slightly higher in the topotecan arm. So too are delays, interruptions, and dose reductions, 65 percent for topotecan and 44 percent for Doxil.

Here we see the percentage of patients with adverse events by severity. The yellow bar shows Doxil and the pink bar shows topotecan. You can see that for both groups the majority of patients get mild to moderate events. Doxil is associated with slightly fewer events at grade III but significantly fewer, less than .001, for grade IV.

To illustrate the comparative safety a little bit further, what we've taken here are Doxil's five most frequent adverse events and compared them

with topotecan. What you can see is that, of course, PPE is the commonest event for Doxil, the majority getting mild to moderate. Eighteen percent here get grade III. One patient is reported as having grade IV. Stomatitis the second commonest. Again, mainly mild to moderate.

But for the remaining three events, there are more topotecan patients who experience these particular events. In particular, I draw your attention to anemia where many more experience grade III and IV anemia.

Here we have done the reverse. We're look at topotecan and the top five topotecan adverse events. The striking thing is that these are mainly hematological as one might predict and that there are fewer grade III, IV events denoted with the dark and mustard color for Doxil or the darker red color for topotecan. There are many fewer grade III, grade IV events for Doxil versus topotecan.

Focusing on neutropenia for a minute, in the neutropenia here there were 13 neutropenic cases reported with topotecan versus none reported with

Doxil. Also, there were two deaths associated with neutropenic sepsis in the topotecan arm, and no drug related deaths with Doxil.

Looking at alopecia 56 percent of patients had hair loss with topotecan. Seven percent had total hair loss. 12.5 percent had hair thinning with Doxil. There were no cases of total hair loss.

In summary, we would summit that Doxil is generally well tolerated. It is associated with relatively mild myelosuppression and minimal alopecia. PPE is the most common adverse event that is manageable and that is evidenced by the relatively low number of patients who actually withdraw as a result, 3.5 percent.

The adverse event profile is predictable. That's based on the similarity in adverse events in the total solid tumor patient population, the Kaposi's sarcoma population, and also the three years marketing experience that we now have.

Thank you very much. I would now like to hand the podium back to Ed Schnipper who is going to make some concluding remarks.

DR. SCHNIPPER: So what is the value of Doxil in this patient population? First, Doxil meets an unmet medical need for patients for whom there is no approved therapy. It has an objective response rate of 14.4 percent in these highly refractory patients the duration of response being almost 10 months. It's generally well tolerated and has convenient monthly dosing. Doxil is dosed with a one hour infusion once a month through a peripheral vein since stop was vesicant. It's less intrusive than many other therapies in patients' lives.

In conclusion, Doxil is active in patients with ovarian cancer who are refractory to platinum and paclitaxel and who also may be refractory to topotecan. Doxil represents a valuable addition to the treatment options for these patients.

Thank you and we'll be happy to take your questions.

DR. DUTCHER: Thank you for a very concise and ahead-of-time presentation.

Are there questions from members of the committee? Dr. Ozols.

DR. OZOLS: The committee is going to have to try to answer the question of whether Doxil has really a meaningful therapeutic benefit in this group of patients. You're talking about a drug that produces a response rate of about 10, 12, 14 percent with as many patients dropping out because of toxicity as well.

You've got to face a situation where patients, as Maurie pointed out, are living longer. You have many patients who don't have symptoms who do have active disease and does a partial response really make much difference to them?

It's doubtful that you're going to impact on survival with that kind of a response rate in that group of patients. When we look at therapeutic benefit, we have to ask several questions like who really is going to benefit. I think it's not the challenge of saying whether this drug is active or not. This drug definitely has some activity. I think we are seeing objective responses. There are some issues of trying to figure out where best to use this drug.

One of the things is when you talk about refractory, you have a 10 percent response rate in patients who actually progress on disease and that's the worst group of patients. Do you have any responses in patients who progress on their initial treatment with paclitaxel and platinum?

I mean, we talk about progressing on disease. That could be progressing on second-line treatment of platinum or paclitaxel. But do you have any patients in that 20 percent or more you pointed out who don't respond to initial treatment? Do they respond?

DR. SCHNIPPER: We haven't specifically broken the data down that way. We have responses on patients who have progressed on their last platinum, on the platinum they had just before they took Doxil.

DR. OZOLS: And that's a different group of patients.

DR. SCHNIPPER: Right.

DR. OZOLS: Because the worst group is still the patients who get their initial paclitaxel, carbo-platinum, whatever, and then progress on that

disease. In that treatment do they respond at all? Because I'm trying to figure out who shouldn't get the drug. I think because of the toxicity that we're seeing and the limited activity, certainly I think we need to give some guidance to the clinicians about where to use it and where not to use it.

DR. SCHNIPPER: I don't have specific information on that particular group of patients. We have patients who have progressed while on platinum after as many as five different regimens. We also have patients who --

DR. OZOLS: That's a touchy issue about patients who have had lots of regimens. Patients who have had many regimens and continue to be treated with multiple regimens, you are selecting out a group of patients who actually have a better overall prognosis. When you say it's the worst group of patients because they've had more than three or four treatments, in fact, you may be selecting out patients who have a long natural history and, therefore, do reasonably well. It's's really the ones who are going right through treatment are the ones that were --

DR. SCHNIPPER: Yes. You are absolutely right. We were obviously very concerned about that. One of the things we looked at is we looked at the patients who had a longer time to regression on Doxil than their prior regimen. There were actually 23 patients who had more than 90 days longer time to progression on Doxil than their prior regimen indicating that they were not patients who necessarily would have long times to progression on any regimen that they have.

DR. OZOLS: Another questions. Again, trying to figure out who should get it and who shouldn't. Did you really see any therapeutic benefit in the sense of symptom relief? I mean, the patients you're talking about who had symptoms from their disease with a 10 percent response rate, were those symptomatic benefits?

DR. SCHNIPPER: The majority of the patients who entered these trials entered with a very high performance status, as Dr. Markman said. The case support forms on these trials asked for the investigator to evaluate evaluable disease as well as

measurable disease.

Of the responders in the phase through trials, there were five patients who entered with ascites. At the time that they demonstrated response, five out of five had improvement in their ascites. In fact, there was some evidence that patients were feeling better and doing better.

The majority of the patients felt reasonable well when they started so we looked at things like pain medication and other sorts of things. Most of them weren't on pain medication to begin with.

DR. OZOLS: I mean, in ascites you can have a little bit of ascites picked up on CT scan that goes away or you can have massive ascites that goes away. I mean, the symptomatic benefit is still something that still really bothers me a little bit.

The other thing that I'm very concerned about the European study. I mean, that's a group of investigators who are very good investigators who were able to get together to do this study and they had no responses.

Now, you can say maybe that's because the

worst group of patients but, again, that concerns me because in a community you may actually be giving this drug to a worse group of patients than you actually saw in your trials so the community practice maybe reflects more the European practice and then you maybe have no responses. I'm very concerned about a large trial with zero out of 36. That's very concerning that there is no activity in that group of patients. And to say it's because they have worse disease again may be --

DR. OZOLS: We were obviously concerned as well, but we were very much encouraged by the fact that our randomized Phase III trial had results that were very consistent with our overall Phase II results.

DR. SCHNIPPER: But can you again tell in patients if you say that the European data had no responses because they were a worse group of patients, again can we hone in on who shouldn't get the drug? Do patients with bulky disease not respond then? I mean, should you try to --

DR. OZOLS: I can show you some of the

parameters of responders versus nonresponders and show you that there is quite a lot of overlap in terms of responders versus nonresponders in terms of these issues of bulky disease based on characteristics, etcetera.

If I can have the slide on, please. You can see from here if you compare the responders to the nonresponders in terms of the 21 responders in the Phase III trials and the nonresponders, you see they compare pretty favorably in terms of a number of regimens. If you look at drug-free interval, they are fairly close. In terms of platinum-free interval also fairly close because, remember, these studies started in 1994 so some of these patients got platinum in sequence, then Doxil and then topopecan.

The sum of legions was slightly higher in the nonresponders but look at the ranges which overlap quite a bit, as well as the CA-125. I think it would be very difficult for a practicing physician to actually predict from these typical prognosticators who would respond and who would not respond because of the overlap in the ranges here.

DR. OZOLS: And your progression when you patients progress, that was a radiologic progression or physical progression? It wasn't a CA-125 progression?

DR. SCHNIPPER: In the vast majority of the patients there were a few exceptions but the vast majority was radiologic progression, yes. I'm sorry, they were all radiologic progressions.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: I've got a couple of questions. In study 30-49 it looks like, if I got the numbers right, you have about 80 patients that you're looking at that have the double refractoriness and there were about 400 so far in your interim analysis. Is that correct?

DR. SCHNIPPER: No. There's 237.

DR. MARGOLIN: Okay. So there's about 40 percent of the total that are analyzable for fulfilling the refractory criteria.

DR. SCHNIPPER: Correct.

DR. MARGOLIN: The question I have since this is an interim study and you have only partial

accrual, are attempts being made -- is the statistical design of that study intended to allow a completely separate statistical analysis of patients who fulfilled the refractoriness criteria so that at the end you'll be able to look at those patients separately with a robust statistical analysis and compare the activity of the topotecan and the Doxil?

DR. SCHNIPPER: Yes. The patients who were stratified for level of refractoriness at the beginning of the trial so they are priorly set up for that.

DR. MARGOLIN: That's not the same question. Well, we talked about that yesterday. Prestratification for balanced factors between your groups is fine if you're going to look at the data all together at the end. But designing the study II contained purposely enough patients so that at the end you can break out those patients and look at them separately requires more patients than the prestratification.

DR. OZOLS: I'll ask Dr. Allred from our statistical group to answer that specifically.

DR. DUTCHER: Please state your name for the record.

DR. ALLRED: My name is Randy Allred. Yes. This was a planned interim analysis as specified in the protocol. These patients were a subset of the 200 evaluable patients that were stated in the protocol.

The other thing to keep in mind is that all patients are accrued now so accrual is closed. We're just waiting for follow-up time to complete. The study was not powered to show differences in this subset of patients.

DR. MARGOLIN: Thank you. If I could please have one more. This would be more theoretical or future studies. I think Dr. Markman and others in this field have shown us that the patients who in general do the worst are those with measurable disease. That large group of patients who don't have easily followable disease and you can decide what you want to do with the marker are actually more favorable.

If one were to agree based on some of the

things we talked about yesterday, that in certain populations of patients it is appropriate to look at time to progression as an appropriate endpoint as a surrogate for clinical benefit, would that not answer a need that might actually show greater activity for this and other new drugs in ovarian cancer? Are any attempts being made to address that group?

DR. SCHNIPPER: I'm trying to specifically understand your question. Are you asking if we are exploring time to progression as a means of looking at only the measurable disease population?

DR. MARGOLIN: No. Are you doing any studies in nonmeasurable evaluable patients carefully selected ?

DR. SCHNIPPER: No. The entry criteria for all our studies are measurable disease.

DR. DUTCHER: Dr. Nerenstone.

DR. NERENSTONE: Yes. I share some of Dr. Ozols concerns about the toxicity of this drug. I just had a few questions for the sponsor as well. Dosing - this is a pharmacokinetically different drug than we're used to. I want to know did they dose

according to ideal body weight or actual weight? Especially since in the community the patients are going to get this drug are going to have a lot of ascites. They could have pleural effusions and even obesity is sometimes a problem. How are these patients dosed?

DR. CUNNINGHAM: Hello. My name is Ken Cunningham. The patients were dosed according to their actual body weight in fact.

DR. NERENSTONE: One of my other concerns that may relate to that is that even in the Phase III of 44 percent delay or reduction in subsequent doses of the Doxil, having treated some patients and seen PPE, I can't minimize the effect of patients of this side effect.

Do you think that maybe you're at too high a dose? That 50 per meter squared is the first dose might be beneficial but 44 percent dose reduction for other doses leads me to think that perhaps a smaller dose in subsequent because this can be cumulative might be really clinically more tolerable. Has any thought been given to that?

DR. CUNNINGHAM: Well, our plan, of course, is to at the very first signs of grade II PPE 2 dose reduce. If doctors take note and make that first dose reduction early then, in fact, PPE is well minimized. Our particular stance at the moment is to start with 50 but accept that many patients will actually be reducing their dose once they get the first signs of grade II PPE.

What may be of some help is we have done a study where we started a lot higher and we had to dose de-escalate and I would be happy to show the results and how we actually came down and the reduction in PPE with you. Would that help in answering your question?

DR. NERENSTONE: No. I'm just talking from a clinical perspective that as this drug is going to go on market at the appropriate dose, I'm just concerned that the indication is a 50 per meter squared for each dose and that may just be really too high. When you require 44 percent of patients to dose reduce in a well controlled trial of people who are used to giving this drug, it makes me a little

concerned that when it goes out to market where clinicians are not as familiar with the side effects, that you might actually be overdosing these patients.

DR. CUNNINGHAM: I think the one thing that I would like to comment on is, as I showed you in the presentation, the majority of patients even at cycle VI were receiving 90 percent of their intended dose intensity. A lot of patients might actually have a dose modification but it's actually relatively small and doesn't impact enormously on the absolute dose.

The other thing to say is that 44 percent aren't dose modifying for PPE. It's probably about 20 percent of patients who get PPE dose modified. There are other reasons for dose modification.

DR. NERENSTONE: And one other clinical question. Because this is looked at as really almost a continuous infusion of Doxil, if patients require neupagen or support of their white count, when do you give it and are you going to have any guidelines to help the clinicians with that?

DR. CUNNINGHAM: Well, you saw from my slides that only four percent of patients actually had

growth factors. Clearly you're right in alluding to the longer half-life and there being a rationale for delaying the introduction of growth factor.

At this juncture we cannot give precise information in the PI as to when that should be but we would certainly be suggesting probably out at four days or four days plus.

DR. DUTCHER: Dr. Santana.

DR. SANTANA: I have two questions. One hopefully will be simple and the other one you can give me more data. And that is trying to address this issue that Stacy was presenting which is what is the true equivalency of this product to doxorubicin in terms of milligram per milligram?

Obviously you are putting in more molecules of doxorubicin in the liposome than you are with free doxorubicin. I ask that because one of the slides that you showed us, which was a xenograft model in which you did a study of saline versus Doxil versus Adriamycin.

The dose of the product was the same as Adriamycin, 6 milligrams per kilo and that is very

misleading because in essence you ought to be giving more molecules of doxorubicin and the Doxil than you are with free doxorubicin. If you could address that issue of equivalency of doxorubicin units.

Then a follow-up question regarding toxicity is that I've heard comments that patients with this disease can have long periods with disease with relatively good survival. In the patients who had a response, do you have any chronic toxicity data? That is, in those patients who responded that you followed for long periods of time, are there any issues of chronic toxicity, particular cardiac?

DR. SCHNIPPER: I'm going to start with the second question first if I may. I'm going to ask Dr. Franco Muggia to make some comments on that since he has some of the longest experience following some of these patients.

DR. MUGGIA: I'm hearing some misconceptions about the toxicity that one observes with this agent. For one, when you see the degree of neutropenia and anemia you have to consider the baseline characteristics of these patients. These are

heavily pretreated patients. In fact, out of 52 patients that we treated at the University of Southern California we analyzed the data and anemia is a prognostic factor for survival. So a lot of the patients come to this trial anemic. The anemia that you see there reflects disease more than it reflects the effect of the drug. I think the toxicity of the drug as you saw was PPE and mucositis

In our experience grade IV neutropenia was not present in the overall experience as you saw that grade IV neutropenias are very few and far between and probably reflect a lot of prior treatment. When you see this topopecan versus Doxil trial, then you see the events of grade IV neutropenia as few.

The issue of GCSF is really not strictly relevant to this drug and it is not something I had to use in my experience of three consecutive trials of Doxil.

Now, when it comes to the cardiac toxicity, I think I can expand on that a bit as well. We have looked at 21 patients that received in our Phase I to III trials. These are not all ovarians.

They include all diagnoses. We've looked at 21 patients that have exceeded 500 milligrams per meter squared, 500 or greater.

Our of those they have received a median of 770 milligrams per meter squared of Doxil. We have looked at the serial ejection fractions. In fact, there were only three that have ejection fractions that dropped more than 15 percent. Two of them had received prior free doxorubicin and one's ejection fraction was actually measured in another facility.

We have no incidence of congestive heart failure except that one patient that was shown in one of the slides. One patient that received 990 plus milligrams per meter squared was a patient that had renal disease and hypertension and was on beta blockers. Not a picture of cardiomyopathy. She developed probably in-stage renal disease which was a complication of her preceding cisplatin therapy.

So I think there is a misconception that patients are dropping off because of toxicity. They are not. They are dropping off because of progressive disease. The patients are entered with a variety of

treatments up front so they are a heterogenous group. Some can withstand all kinds of treatment. Others are much more frail but it is progressive disease that really leads to the drop off.

The PPE is a problem of the first two or three cycles. Once you make the dose adjustment, the PPE is not a cause for drop off. In fact, it was very rare that a patient was not continued. I can site you anecdotes of two grade III or IV toxicities that went on to receive the drug for two years. They have PPE on the second cycle and then they went on and got two years of treatment.

It's a problem that probably there is a learning curve. I think with a lot of education when one starts with 50 and then looks at the next dosing, whether it is safe to give the next dose at 50 or dose reduce I think it is something that is strictly manageable.

In terms of clinical benefit, I think these are difficult issues, but I can site you a number of patients where the interval to some disease related event which required treatment or surgical

intervention was short. Then they went on Doxil and stayed on Doxil for a longer period of time than the two or three events before. There are several patients like that and to me it reflects clinical benefit.

DR. OZOLS: We need to clarify that about patients dropping out because of adverse events. I mean, the sponsor just said that patients are dropping out at about a 20 percent rate because of adverse effects. You're telling us that people weren't dropping out because of adverse effects.

DR. CUNNINGHAM: The overall withdrawal due to adverse events was, in fact, 11 percent and 3.5 percent was accounted for by PPE.

Slide on, please.

You can see from this slide here which I showed in the main presentation that is the situation. The denominator when I was talking about patients who actually had PPE, this denominator here reflects the 396 overall ovarian patient population denominator, hence the discrepancy. But 3.5 percent of patients out of all those ovarian patients actually withdrew as

a result of PPE.

DR. SANTANA: Answer the equivalency question.

DR. SCHNIPPER: Yes. I meant to get back to that question. I'm going to ask Dr. Frank Martin to address that.

DR. MARTIN: Just to clarify, in all of the preclinical models when we talked about milligrams of doxorubicin injected, they were equivalent. That is, doxorubicin is equivalent. In comparison, for example, 8 milligrams per kilogram, that was an absolute number of doxorubicin administered to the animal. Those were identical injected doses.

Now, if you're interested in knowing what the activity of Doxil is relative to Adriamycin, in a way to sort of define the therapeutically equivalent dose, I do have information on that in one animal model if you would like to see that.

Slide on, please.

This is a Lewis lung tumor model. Again, a typical growth curve, tumor size versus time after implantation. What we did here was we dosed the

animals with the maximum tolerated dose of Adriamycin. In other words, at any higher doses of Adriamycin these animals would experience toxicity that was unacceptable. You can see there is activity. Adriamycin at its MTD is better than the saline control.

We then took Doxil from the same administered dose, 9 milligrams per kilogram, and diluted it down, titrated it down to 5 milligrams per kilogram, and tried to arrive at the dose that showed approximate equivalence. As you can see in this model, one milligram per kilograms of Doxil provided about as much antitumor response as 9 milligrams per kilogram of free doxorubicin.

Now, this was not the case in all models but of all solid tumors we tested in this manner, the improvement in terms of antitumor activity ran from about 2.5 fold up to 9 fold.

DR. DUTCHER: I have a question. Just in looking through some of the data, it looks to me that the median number of treatments in the Phase II studies were really two and the median duration of

cycles was either two or three. In the European study it was essentially one. So the evaluation of disease was at four weeks, single evaluation? Did the stable patients also come off at four weeks?

DR. SCHNIPPER: The evaluations were every other cycle if the patient stayed on. For patients that had an event, they were documented at that time. If somebody had some clinical event, they would have been documented for that clinical event.

DR. DUTCHER: So it does come back to Dr. Ozols' question of who shouldn't get this drug.

DR. SCHNIPPER: I think since we're talking a lot about clinical benefits, it is probably important to hear some more from a clinician. I'm going to ask Dr. McGuire to make some comments on that and then we'll come back to the actual data.

DR. MCGUIRE: I'll try to be brief. Having used a fair amount of this drug in my own patient population, I think a couple of points need to be made. First, one can't really look at performance status in an ovarian cancer patient like you can in other cancer patients because often times performance

status may go from 80 plus to 40 plus. These patients, to put it mildly, go to hell in a handbag very quickly with valve obstruction, ureteral obstruction, etcetera.

In terms of dropout rate having treated a number of patients on the trial, it's an 11 percent dropout rate and only 3 percent for PPE. But we all know that when we have a patient on a study there are multiple factors that lead the clinician in conjunction with the patient to decide to continue the drug or not to continue the drug.

In a patient that has some skin toxicity, maybe even a grade II PPE who has not met the criteria of a partial response who has stable disease, the investigator may, in fact, take the patient off the study. They can't take the patient off the study because of progressive disease because the patient has not met the criteria for progressive disease so the patient is taken off study for an adverse event. Whereas that same patient, were that patient to have a near partial or partial response, that patient would have been left on the study.

I do think the 11 percent is an excessive or somewhat of an overestimate of true toxicity of this drug. I think Franco even has more experience and those of us that have used a lot of this drug know in the patient that is benefitting from the drug in terms of symptom relief, in terms of some tumor response, that the patient will, in fact, implore the doctor to continue the drug even with some skin toxicity.

DR. DUTCHER: Dr. Krook, you have a comment?

DR. KROOK: Going to the Phase II studies which you based with the refractory patients, I recall a time to progression of 15.9 weeks. Can you give us a feeling of the overall survival of these people a la the discussion yesterday and the fact that these are people who are heavily pretreated?

DR. SCHNIPPER: Yes. I can.

DR. KROOK: In both the responders and the nonresponders.

DR. SCHNIPPER: Let me start off by showing you the overall. If I could have the slide

on, please.

You can see here that if you look in the various populations, the overall survival -- if I could have the next slide, please -- of just the ovarian patients that were refractory. Can I have the slide on, please?

If you look at the refractory platinum and paclitaxel patients, you see the survival there listed as 34 weeks and the triple refractory 38 weeks. Overall for all patients on all intent-to-treat was 38 weeks.

DR. KROOK: In those people who responded, in other words, the time to progression is in the responders, do we lengthen the survivorship significantly compared to the overall?

DR. SCHNIPPER: The answer to that is yes. There is quite a longer time to progression in the responders compared to the nonresponders. We obviously have statistical concerns about looking at respondents versus nonresponders. But if you want to see that curve, we can show that to you.

With apologies to Dr. Simon, we can put

that curve up. If Dr. Simon would just like to turn away for a moment. Since you asked, we'll show that curve. This is the Kaplan Meier curve of responders versus nonresponders with apologies again to Dr. Simon.

DR. DUTCHER: Ms. Solonche, do you have comments or questions?

MS. SOLONCHE: Yes. I do have a couple of questions and comments. These are from the person who has survived ovarian cancer for four years. But these comments are also from the thousands of women who have died from ovarian cancer in that four years.

Regarding the dosing question, I know that science likes to start with the most someone can take and go downward. But from the patient point of view in regard to this particular drug, and probably many others, has anyone considered starting at a lower dose, say 35 milligrams, making life perhaps a little easier on the patient and then increase the dose if things are going well. Or is the concern that at that level of drug the response would be even lower than it is with the 50 or 40 milligram dose?

DR. SCHNIPPER: Well, you've correctly stated the problem. But the answer to your question is, yes, we are studying lower doses. We don't know what the efficacy is of lower doses before we recommend such a thing but we certainly are studying lower doses.

I would like to ask Dr. Gordon to comment on that because he has a lot of experience with some of these trials.

DR. GORDON: We found at this dose it was generally fairly well tolerated as you've heard. My experience with treating a lot of our patients was we began to be more adept at picking up the PPE and making adjustments when necessary.

As you've heard, and we've seen with our patient population, too, most of the PPE if you picked it up early and could take care of it, patients did very well. In fact, in most of our patients it was almost a difficult problem because it occurred later on in the course as a cumulative dose in patients who are responding.

Our patient population if we tried to dose

reduce them, they were actually fairly concerned about the fact that we might be decreasing efficacy in a responding patient. We often had to talk the patients into a dose reduction at the later cycles.

MS. SOLONCHE: Well, my problem with that is that, you know, you can say that, okay, only 3 percent had a PPE reaction and only 4 percent had another toxicity reaction. If a woman is taking this treatment and she has maybe stage I reactions in five different areas rather than stage II reaction to two areas, you know, whatever combination, that woman is going to have a more difficult time. Is there a way that you have sorted this out individually and then cumulatively to see the patient reaction?

DR. DUTCHER: Well, most of the studies do have dose reduction schedules for that. I think that you can --

MS. SOLONCHE: Right, but --

DR. DUTCHER: Everyone got the first three doses.

MS. SOLONCHE: Right. But if you have a mild reaction in one area and you have a mild reaction

in another area, you put those all together and you feel less than good.

DR. DUTCHER: I don't mean to argue with you but I think many of the toxicity grades that we use in judging drugs are purely laboratory abnormalities or other things that are not likely to be associated with symptoms. I think the safety of this drug would suggest that a patient who has four grade I's is unlikely to feel bad or to be as ill as a patient who has one grade IV.

MS. SOLONCHE: I don't mean to make this very personal but have you ever had chemotherapy?

DR. DUTCHER: No. But these are the kinds of things that you learn to deal with as a physician. They can certainly give you a schedule in the package insert that would tell what dose reductions might be appropriate. As you probably know, there's a learning curve. They have gone up and down the dose range with this drug and I think have a lot of information in well over 2,000 patients of varying illnesses who have taken this drug.

DR. GORDON: Most of the dose reductions

that were done were done because of the patient's toxicity much more so than laboratory toxicity in the study. The neutrophil counts was a minor issue. It really was the PPE and stomatitis were major causes of the dose reductions. When these interfered with the patient's capabilities to continue, then dose reductions were performed to make it easier for the patients to tolerate.

MS. SOLONCHE: I also want to go back to something that was mentioned yesterday ad nauseam. The idea that time to progression is the indication that you look at, whereas from the patient perspective we are looking at survival and I don't think we have enough data on that at the moment to see this as a drug that is going to advance treatment in a great way.

DR. SCHNIPPER: I'd like to finish answering your other question first. That is, in terms of the side effect profile of Doxil, I think it's important to keep in mind that these trials were started in 1994. This represents the sum total of all our experience included our early experience. This

represents probably the worse case scenario before our learning curve.

If you look at the incidents of some of these side effects now versus 1994 at most of the sites, and I think any one of my colleagues here would agree, it's significantly less.

Let me address your other concern about the time to progression versus survival as an endpoint. I think it is important to keep in mind that we are here to talk about accelerated approval for Doxil. Accelerated approval means that we will come back later with survival data from randomized trials.

In fact, we are ahead of the curve in some extent because I have already given you a peak of what is to come from the randomized Phase III trial indicating activity in that trial. The whole idea of the accelerated approval process, at least as I understand it, is to bring drugs forward with reasonable likelihood that they would benefit patients with subsequent proof to come.

DR. DUTCHER: Dr. Schilsky.

DR. SCHILSKY: I'm curious to know, you've shown us some data on estimates of tumor bulk and responders and nonresponders. Can you tell us how those data were derived? How was tumor bulk estimated in the patients in this study?

DR. SCHNIPPER: This was a measurement on CAT scan of the total area of measurable lesions.

DR. SCHILSKY: And was that done by investigators at the site or was it done by the independent review panel?

DR. SCHNIPPER: It was done by the investigators at the sites and then reviewed by the independent panel.

DR. SCHILSKY: And I'll tell you in a minute why I'm pursuing this. Do you have a sense of what the level of concordance was between the site reviews and the independent reviews?

DR. SCHNIPPER: Yes. I do. The level of concordance was quite high. It was also interesting to note that they were responders that were picked up by the independent radiologic review that were not picked up by the investigators in both ways.

Of the patients that were available for review -- and if I could have the slide on, please -- the level of concordance was quite high. The overall response rate by the investigator was 21.3 percent and was 17.3 percent after independent radiologic review of available CAT scans. We felt quite validated. And keeping in mind that it went both ways. We feel that the data is quite solid.

DR. SCHILSKY: So it would be reasonable to conclude then that an investigator at a site or the radiologist at that site would be able to estimate the tumor with a reasonable degree of accuracy within the difficulties inherent in doing that, I guess. What I'm trying to get at is the question that Bob Ozols started the session with, which is it seems pretty clear that there is activity of this drug.

The question is is there any way of defining which patients are most likely to benefit from it because it does seem to have activity but it only seems to have activity in a small percentage of all of the patients who were exposed to it. Ovarian cancer is one of the few solid tumors in which we've

traditionally given some credence to the ability to estimate tumor bulk.

One of the things that you showed us in showing us the characteristics of responders versus nonresponders is that while there is some overlap, there were, for example, no responses in any patient who had a tumor bulk estimated greater than about 100 or 105.

One of the things I'm wondering about would be if it is possible to reasonably and reliably estimate tumor bulk, and recognizing this is still a small sample size, even if one, you know, sort of doubled that upper limit, could one reasonably say that a patient has a tumor bulk in excess of some number, that the probability of that patient responding would be exceptionally small and, therefore, perhaps provide some guidance to clinicians in who is most likely to benefit or who is least likely to benefit.

DR. SCHNIPPER: I'm going to ask Dr. McGuire to make some comments. Before I do, I think it's clear to say that with tumor bulk as a

prognosticator, that would probably be true of any drug.

DR. WILLIAMS: I'd like to make a comment also. I'm a little concerned about the quality of the data for this analysis because I do know that back and forth on this issue that the number of lesions versa the number of measured lesions used for determining a response might not be the same. It may just be just a coincidence or a random matter how many lesions were actually measured leading to what we're calling tumor bulk. I agree that if perspectively determined it might be an interesting question.

DR. MCGUIRE: Well, I wish it were that simple in ovarian cancer. I think what we all know is that what you see on the CT scan is the tip of an iceberg. Some of these patients that have bowel dysfunction that get explored for bypass of bowel obstruction, there's almost always a lot more tumor than meets the radiologist's or the clinician's eye.

What we really have to make judgment on is really patient symptoms. I think that often, although we can't prove it, that the low response rate in the

European study that was done was maybe due to the fact that in contradistinction to this country, often time treatment is withheld until the patient actually has significantly symptomatic recurrence of ovarian cancer.

Often times, as I've already alluded to, these patients bowel obstruct fairly quickly. This is not a drug that works in one week or two weeks. If you wait too long to initiate therapy, I agree with you that you are less likely to respond. I'm not sure that one can prospectively pick up that patient population based on sum of lesions.

For example, a patient may, in fact, have a huge pelvic mass that meets the criteria of greater than 100 square centimeters and be asymptomatic from it and would take that patient unperturbed weeks to months to actually develop a bowel obstruction.

There may also be a similar patient you has eight or 10 one centimeter lesions that are conveniently placed in cirrhosal surfaces on the small bowel that is under 100 centimeters and that patient may bowel obstruct within one month of that first

evidence of CT progression.

I think it would be nice, but I think it's true with all of the second-line and third-line drugs that we use whether it's topotecan, or I guess I should have mentioned other drugs since they are not FDA approved but which we clinicians use. It will is hunt and peck on the typewriter in terms of taking a patient.

The only ones we tend not to use are oral agents and patients that have significant bowel dysfunction because of concern that they are not getting the drug into the systemic circuit. I don't know but Maurie has a lot of experience and may also want to add to that.

DR. MARKMAN: Thank you. I really feel that it's important to comment on a very important issue in the clinical trials arena. That's not the discussion today but one of the problems is there's a serious dislink between how we objectively measure response from something that we can measure on a CT scan, particularly in ovarian cancer.

I would agree with Bill that this is a

very difficult disease to do that because of the abdominal cavity. That population that we can actually enter in one of these trials may very well be the population we cannot ask the question that Bob asked which is clinical benefit.

Just because that patient has that mass that we can measure, they may not have any symptoms. I would submit we are actually looking at a very small part of the population when we do the typical clinical trials we do for drug approval.

A typical patient with ovarian cancer we see later in their course is that patient who has a variety of vague but important symptoms, clearly has disease, has an elevated CA-125, that's a patient you would like to measure clinical benefit but would never be on one of these trials because they don't have that measurable disease category or they don't meet some of the other criteria because they've had too much therapy.

That is really where you can get at this true question of clinical benefit which I agree 100 percent with Bob is the question we want in which the

cancer patient population wants to know about.

I personally believe we should expand the trials and include that population but that's not the population you are discussing today. It's hard to say where is the evidence of clinical benefit when, in fact, the people you put on the trial were just there because they happened to have measurable disease.

I'll go further than that to say that I think that's a very important population than what I'm talking about. I have actually used this drug in that population in my own trials that would never meet the criteria of the FDA because they are based on other criteria. It is an active drug that does have patient benefit associated with it. Patients do feel better and it's a tolerable drug.

But I think it's very hard when you ask that question in a population of patients on these trials that very well don't have those kinds of symptoms where you can really directly address the question because that's not the question. It's you got a mass and does it shrink. I think it's very hard to put those two together and it's, therefore, very,

very difficult to ask that question of clinical benefit in this setting unless you go beyond the trials that are designed the way they are.

DR. DUTCHER: Dr. Simon.

DR. SIMON: I mean, I think that's right but I think sort of the presentation has it exactly wrong then because the FDA is not biased to wanting measurable disease. The FDA wants to see clinical benefit. We haven't really had any presentation of any kind of clinical benefit. There's been no evidence of symptom relief. It's hard to see how the 15 percent response rate translates into changing the course of disease in any of these patients.

I guess my specific question is we're being asked for a recommendation with regard to accelerated approval which I guess the basis -- that is, do we believe this 15 percent response rate is a reasonable basis for expecting that will translate into clinical benefit on other trials that the sponsor will do.

I personally question whether a 15 percent response rate is likely to translate into a survival

benefit. What trials is the sponsor going to do if they are granted accelerated approval? What trials are in process that will demonstrate clinical benefit and what will be the logic?

If you're talking about your current randomized trial against topotecan, I can see two problems with that. One is you are probably only going to have 80 patients who are doubly resistant to platinum and, I guess, taxel. That's going to be a fairly limited number.

Secondly, what is the logic going to be? Are you going to show better survival than topotecan? If you show equivalent survival to topotecan, are we then supposed to believe that topotecan has a survival benefit in that set of patients? What are the trials that you are going to do and what is the logic that you are going to demonstrate clinical benefit?

DR. SCHNIPPER: I'd just like to make a few comments and then I'll ask Dr. Cunningham to make some additional comments.

The first comment, of course, is that these trials were discussed with the agency obviously

before I initiated them so there was some concurrence there about measures.

Secondly, the number of patients on the total population that are refractory in the Phase III trial would probably be more like double or a little bit more than what you've seen there because this is only half of the population that has been accrued so it would be a much larger group.

DR. SIMON: I meant 80 per arm which is double what you have now which would still probably not be sufficient.

DR. SCHNIPPER: And, of course, there are additional measures in those trials that were pilot in Phase II but not reported on because they were just pilot in terms of quality of life measures, etcetera, that are built into the Phase III trials that were not built into the Phase II trials.

DR. WILLIAMS: I'd like to also comment, Dr. Simon, that we certainly had at times entertained the Phase IV trial being in a setting similar to but not identical to the setting for the accelerated approval. It's quite possible we would consider a

significant clinical benefit in the setting of second-line. We might consider that to be adequate for meeting the purposes of fulfilling the Phase IV requirement for this indication.

DR. SIMON: What would have to be shown in second-line?

DR. WILLIAMS: Basically clinical benefit by whatever means the sponsor fulfills that requirement. Certainly survival. But I --

DR. SIMON: Superior to topotecan or equivalent to topotecan?

DR. WILLIAMS: I'm not talking a specific trial at this point in time. If one could show equivalents to topotecan for clinical benefit and show that the increment of clinical benefit had not been lost in that equivalence comparison, that would be theoretically possible. But certainly superiority would be a much more practical consideration.

DR. CUNNINGHAM: If I may just give you some details on the current study. It's a 460 patient study in over 100 centers. The study stratifies for refractory patients versus nonrefractory patients.

The primary endpoint is tied to progression. Of course, we also monitor response rate and survival.

The study has, as I said, been completed but we are now going through the process of analysis and that will be sometime before that full analysis has taken place. We estimate that the number of refractory patients should approximate half the patient population.

DR. DUTCHER: One left.

DR. OZOLS: Maybe during a break you can come up with this number, but I still think it's important to know again who we can use in what objective manner and one is how patients have responded. I think you talk about a 10 percent response rate of patients who had progressed their disease while on treatment. I suspect most of those patients are patients who progressed on second-line treatment.

The real question then is how many patients who never responded to any other treatment responded to this? Do you have patients who have -- you know, if I give a patient taxel-carbo and they

progress, what is the response rate in that group? If I give them taxel-carbo and they progress, they get topopecan and progress. I suspect it's less than 10 percent. Are there any responses in patients who never respond to anything else?

DR. SCHNIPPER: I don't have that information. I'll try to get that for you.

DR. DUTCHER: Thank you. I think we better take a break. Come back at 10:05.

(Whereupon, at 9:44 a.m. a recess until 10:06 a.m.)

DR. DUTCHER: We're going to proceed with the FDA presentation. Dr. Frykman.

DR. FRYKMAN: Dr. Dutcher, members of the committee, FDA colleagues, ladies and gentlemen, it is my pleasure on behalf of the FDA to present the agency's highlights of the review of SNDA 50-718. Like any worthwhile undertaking, there are a number of talented individuals whose talents combined to produce a very good review.

Two people I would like to acknowledge in particular are Grant Williams for his leadership and

Alvis Dunson. I think the company would join me in acknowledging Alvis' effort in keeping the entire review project coordinated.

The specific proposed indication, as you've heard, is that Doxil is indicated for the treatment of patients with metastatic carcinoma of the ovary who are refractory to both paclitaxel- and platinum-based chemotherapy regiments and who may also be refractory to topotecan.

In this case, refractory is defined as patients having progressive disease while on treatment or within six months of completing treatment with the two above regimens. The agency has determined that the text in brackets is probably -- the number of patients to base that indication on is probably too small and, therefore, will not be further considered.

Under the federal regulations outlining the accelerated rate approval mechanism, there are two requirements that must be met. The first, that treatment provides benefit over "available therapies."

The exact definition for this application is that there are either drugs labeled for or with a

large body of literature supportive of efficacy for ovarian cancer refractory to platinum and paclitaxel. In this case the FDA has determined that there are no available therapies. Further information about this will be forthcoming in a guidance document soon.

The second requirement is that approval be based upon a surrogate endpoint that is reasonably likely to predict clinical benefit. In this case, that surrogate would be objective tumor response. Therefore, the committee has quickly come to the conclusion that the question that is going to be asked is whether the data presented by both the sponsor and the agency on objective response indicate that Doxil is reasonably likely to be associated with clinical benefit in this population.

In order to begin to answer that question, from the agency's perspective let me just briefly outline again the four trials that you've heard already presented from the sponsor. Three of the four studies were Phase II, the single Phase III study, and the last in chronological order, the last Phase II study are currently close to accrual but are still

maturing the data.

The schedules that were used in the four trials were different. Three of the trials, the last three, had a four-week schedule. The first trial was an every three-week schedule.

Two of the studies were completed completely in the United States. One is being done both in the United States and Europe. The single study that we've heard about, study 47E, is being conducted and was conducted solely in Europe.

To begin with, the efficacy review. I won't point out too much on this slide except for the fact that this was the every three-week schedule. A total of 35 patients were accrued to this study and the population targeted for enrollment was platinum and paclitaxel failures.

The agency's methodology in review was to use the primary electronic data presented by the sponsor. In this case each patient's case was reviewed to determine its platinum and paclitaxel refractiveness. Of the 35 patients enrolled, 27 were found to meet the above criteria.

The serial tumor measurements then that were listed for each patient were reviewed looking for confirmed responses. That is, responses that were noted to have occurred at a time point and then four weeks later. Of those, six of the 27 patients were found to be meeting the criteria for a response rate of 22 percent. The confidence intervals shown here range from 9 percent to 42 percent at the upper 95 percent bound.

The next study, 30-47, again you've already heard about that so I'll make these comments brief. This was on a four-week schedule. A total of 89 patients were enrolled into the study and of those 89 82 were found to be both platinum and paclitaxel refractory.

The serial tumor measurements were again reviewed as in the prior study. Of those 82 patients that were platinum and paclitaxel refractory, 14 were found to have been meeting the criteria for response for a response rate of 17.1 percent, 95 percent CI ranging from 10 to approximately 27 percent.

The third study that was reviewed only in

brief by the agency was that of 30-47E. The study was conducted only in Europe. Again, it was a Phase II single arm open label study. The schedule used was every four weeks for six cycles. At the time of data submission 52 patients had been enrolled into the trial. Of the 52 patients that had been enrolled, the sponsor determined that 36 of the 52 had met the criteria for platinum and paclitaxel resistance.

The FDA accepted the sponsor's results without detailed review stating that zero of 36 patients were responding to Doxil under the schedule. 95 percent CI ranges from zero percent to 10 percent in this viewgraph.

The last study I would like to review is study 30-49. This was their only Phase III randomized trial. The study population was slightly different as opposed to the Phase II trials in that it was just platinum based chemotherapy for which the patients had to be refractory to. Targeted therapy was for one year and the primary endpoints were timed to progression and response rate.

At the time of data submission or at time