DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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C O N T E N T S

C O N T E N T S (Cont'd.)

NDA Supplement 29-449/S-005 Taxotere (docetaxel) for Injection Concentrate Rhone-Poulenc Rorer Pharmaceuticals

P R O C E E D I N G S

Call to Order, Opening Remarks and Introductions

DR. DUTCHER: Good morning. This is the Oncologic Drugs Advisory Committee, so you all know you are in the right place. We are missing a couple of members of the Committee because they got stormed out in the Midwest. They are still waiting for airplanes, so they will be here by mid-morning, Drs. Krook and Schilsky.

I am Dr. Dutcher. I am chairing the meeting today, and I would like to go around the table and ask the members of the Committee and the people sitting at the table to please identify themselves and where they are from. Let's start with Dr. Swain.

DR. SWAIN: Sandra Swain, Washington, D.C.

DR. SCHER: Howard Scher, Sloan Kettering in New York.

COL. SCHULTZ: Jim Schultz, patient representative.

DR. LAMBORN: Kathleen Lamborn, University of California, San Francisco.

DR. OZOLS: Bob Ozols, Fox Chase in Philadelphia.

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

DR. SLEDGE: George Sledge, Indiana University.

MS. BEAMON: Carolyn Beamon, Sisters Network,

consumer representative to the Committee.

DR. MARGOLIN: Kim Margolin, City of Hope, Los Angeles.

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

DR. ODUJINRIN: Wode Odujinrin, Medical Officer, FDA.

DR. JUSTICE: Bob Justice, Acting Director, Division of Oncology, FDA.

DR. DUTCHER: Thank you. We are now going to ask Dr. Somers to please read the conflict of interest statement.

DR. SOMERS: Thank you. I would like to welcome you all here this morning, and please remind all speakers to use the microphone for the benefit of the transcriber and the people in the back.

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 for the meeting and all financial interests reported by the participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for a conflict of interest at this

meeting, with the following exceptions:

Full waivers have been granted to Dr. Robert Ozols, Dr. Sandra Swain and Dr. George Sledge, Jr. A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12-A30 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Swain has interests which do not constitute a financial interest in the particular matter within the meaning of the 18 USC 208, but which could create the appearance of a conflict. The Agency has determined, not withstanding these interests, that the interest in the government and Dr. Swain's participation outweighs the concern that the integrity of the Agency's programs and operations may be questioned. Therefore, Dr. Swain may participate fully in today's discussion and vote concerning AD32.

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

With respect to all of the participants, we ask in the interest of fairness that they address any current or

previous involvement with any firm whose product they may wish to comment upon. Thank you.

DR. DUTCHER: Thank you. We are now going to proceed with the open public hearing. We have two people who have requested to speak. We would ask them to identify themselves at the microphone, and please state whether or not they have any financial reimbursement from the sponsor. Thank you. The first is Mr. Thomas Cavender.

Open Public Hearing

MR. CAVENDER: Good morning. I am Tom Cavender, and I live in Sarasota, Florida. If it weren't for Dr. Wehle, Mayo Clinic, and Anthra Pharmaceutical I wouldn't be here today. During a routine physical examination in 1987, blood was discovered in my urine, and I was referred to Dr. Barzell, a leading urologist in Sarasota. After performing certain procedures, it was determined that I had bladder cancer.

My first treatment was mitomycin. The cancer progressed and developed into a carcinoma in situ. The treatment was changed to BCG, which seemed to eliminate the cancer temporarily. My visits to Dr. Barzell continued every three to five months for cystoscopies, biopsies, and additional treatments. The BCG seemed to arrest the cancer until late 1995. Subsequently, the treatment was changed and I was given 15 interferon sessions which were completed

in May of 1996.

Biopsies confirmed that the problem was still there, and Dr. Barzell recommended removing my bladder, with all the dire consequences and ramifications. At that time I sought a second opinion from Dr. Wehle of Mayo Clinic, Jacksonville, Florida. After reviewing my x-rays and records, Dr. Wehle agreed with Dr. Barzell. However, he said that Mayo was involved in an experimental study with Anthra Pharmaceutical. Dr. Wehle explained the risk of cancer spreading to other parts of my body, but said that the risk would be less at my age. I am 78 years old and a get a lot of that.

Anthra accepted my case and treatments were started in July of 1996, completed in August of 1996. There were six treatments, and since then I return to Mayo every three months for either cystoscopies or biopsies, whichever is specified in the study. I am scheduled for another biopsy this month.

In almost two years there has been no sign of cancer. Consequently, I have not had to change my physical habits or my lifestyle, for which I am grateful. Anthra Pharmaceutical invited me to tell my story here and are paying my expenses. However, my testimony would be the same under any circumstances because I wanted you to hear how my life would be totally different without this drug.

I wish to thank Dr. Wehle, Mayo Clinic and Anthra Pharmaceutical for including me in this successful program. I urge you to expeditiously approve AD32 so that other patients may share my good fortune. That is it.

DR. DUTCHER: Thank you very much. Thank you, Mr. Cavender. The next speaker is Miss Blanche Holmer.

MS. HOLMER: Hello. My name is Blanche Holmer. I want to talk to you about my bladder cancer, but more important to me, I want to talk about the fact that I have been without the disease since early 1995. Anthra Pharmaceuticals paid my airplane ticket from Idaho Fall, Idaho so I could be here at this meeting today.

I told the folks from the drug company that I wanted a chance to let the other people know how my participation in the clinical trials of AD32 has prevented me, up until this very day, from reoccurrence of bladder cancer.

Early in 1992, I experienced a lot of blood in my urine. I didn't have any signs or symptoms that would tell me that I was having bladder problems, just a lot of blood and some pain. I was scared and very worried. I went to see Dr. Peter Canon, in Idaho Falls, the urologist who had been helping my late husband with his prostate cancer. After doing some tests and x-rays, he let me know that I had cancerous tumors in my bladder and, lucky for me, it had not

eaten through the lining in the bladder. The doctor told me that surgery could remove some of the tumors but that I would need some treatments with a drug called BCG.

In March of 1993, I started the first of six treatments once a week with BCG. I didn't have any problems with these treatments, except that when I came back for a cystoscopy in June, my doctor told me that the tumors were still in my bladder. Right away, I had another series of BCG treatments, from June until August of 1993. This time I didn't tolerate the treatment so well. I ended up with fever, chills and a general feeling of achiness that took a few weeks to go away.

In June of 1994, I was very disappointed when, after the biopsies during that month, I learned that the tumors had returned, and now the disease had affected my left ureter. My doctor thought that the best thing to do was to remove my left kidney and ureter as it wasn't working due to the blockage at the entrance of my bladder. My kidney was perfectly healthy but not working. Surgery took place in July of 1994. Dr. Canon assured me that God had given nearly everyone two kidneys but we really only need one kidney if it is working well, and it will keep us healthy.

I thought about what the doctor said and I wondered what if the bladder cancer comes back? I knew

after reading about it and talking to my doctor about it that I didn't want to lose my bladder. Unlike kidneys, God only gives us one bladder. I didn't want to wear a bag instead of having my bladder. I wanted to do anything to keep healthy, happy, and disease-free. My worst fears came true in December of 1994, after three positive urine cytology results that month, and a biopsy showed that the tumors were back in my bladder.

I had the options that would be available to me now. Luckily, Dr. Canon knows Dr. Richard Middleton, and he talked with him. He told Dr. Canon about a new drug, AD32 treatment at the University of Utah. I thought about the long drive to Salt Lake City from Idaho Falls in the middle of the winter, but considering the thoughts of losing my bladder I knew that I would try the AD32. Every week, for six weeks, from late January till early March in 1995, we drove eight hours round-trip to have this drug instilled in my bladder.

We were lucky with all the traveling in the dead of winter, we had good roads to travel on. I told the study staff that I did like the pretty color, red color of the AD32. Other than the long car trips, the treatments with the AD32 were fairly easy to tolerate. I must say that I did have bladder symptoms around the time of those treatments, and I always ended up with some kind of urine

urgency, and frequently that lasts a while when I am biopsied, scoped or catheterized. It seems to take a few months for the bladder to return to normal after all these types of procedures.

Now we fast forward to today. I am 81 years old, and I am happy to say I still have my bladder. I have enjoyed three years without any evidence of bladder cancer, and I am blessed with a wonderful family. I have two children. My youngest is here with me in the audience today, and I have five grandchildren, twelve great-grandchildren and two great-great-grandchildren. I have spent the last winter in the warmth of Arizona, and now I am enjoying the start of another chapter of my life with my new husband. I was married to my husband, Lewis Funk, in San Diego on May 9, 1998.

I believe in thinking young and thinking healthy. The treatments I received with AD32 have left me feeling healthy. Dr. Middleton and his staff at the University of Utah were just wonderful. I know that I owe them another follow-up visit, but with all of the recent excitement that has been going on in my life, and because I have been feeling so good for so long, I guess I have been putting it off. I am convinced that it was the AD32 drug that got rid of my bladder cancer back in 1995. I am confident when I say that this is the drug that should be helpful to many

more people who have bladder cancer, if doctors could prescribe this treatment.

I represent one voice among the patients with bladder cancer that could not be managed by BCG treatments. Please consider this drug for approval today. I do thank you for hearing my testimony on AD32.

DR. DUTCHER: Thank you very much. We certainly appreciate both of you coming to talk to us and to share your views.

Is there anyone else in the audience that wishes to make a statement before we move on to the next part of the meeting?

[No response]

Then we are going to go ahead and move on with the sponsor's presentation from Anthra Pharmaceuticals.

NDA 20-892, AD32, Anthra Pharmaceuticals

Background and Clinical Data

DR. GULFO: Thank you, Dr. Dutcher. Good morning.

[Slide]

I am Joseph Gulfo and, on behalf of the entire Valstar development team, I am happy to be here with you today to present data for your review and consideration.

[Slide]

Before I begin, I would like to recognize several

experts who are joining us today. Dr. Samuel Cohen, Professor and Chairman from the University of Nebraska, Department of Pathology and Microbiology. Dr. Cohen was a member of the NCI's International Bladder Cancer Project, and currently is on the National Comprehensive Cancer Network, Bladder Cancer Guidelines Committee.

Dr. Barton Grossman, Professor and Deputy Chairman, MD Anderson Cancer Center, Department of Urology. Dr. Grossman is the local Bladder Organ Site Protocol Chairman of the Southwest Oncology Group.

Also joining us is Michael Wehle, a principal investigator of our pivotal studies A-93010/02, from the Mayo Clinic in Florida.

I would also like to thank the FDA review team for their availability and responsiveness, not only in the days and weeks leading up to this meeting but all throughout the development period, including Grant Williams, Wole Odujinrin, Ann Staten, Karen Somers and Leslie Vaceari.

[Slide]

We are here this morning to discuss valrubicin as intravesical treatment for patients with biopsy-proven carcinoma in situ of the bladder that has proven refractory to front-line treatment with bacillus calmette guerin, BCG.

[Slide]

We will have achieved our objectives today if we

are successful in impressing upon you five points that we are thoroughly convinced of. First, by virtue of a slip of felicity, cellular penetration, contact safety, in vitro activity against aggressive bladder cancer cell lines, negligible systemic absorption and local tolerability in animal studies valrubicin is a novel anthracycline that is an ideal intravesical agent for treatment of patients with carcinoma in situ.

Second, bladder carcinoma in situ is an aggressive disease, requiring aggressive treatment of the entire bladder urothelium because the entire bladder urothelium is at risk for occurrence, recurrence, invasion and progression.

Third, for patients with BCG-refractory carcinoma in situ cystectomy is primary therapy. Doctors and patients hunger for salvage regimens but there are none approved, and the agents that are available have not been shown to be safe or effective, indeed, through a proceeding such as this.

Valrubicin is effective treatment for BCG-refractory carcinoma in situ. Complete responses are induced in 21% of patients, with median time to failure or follow-up of 18-plus months. All that translates into meaningful bladder salvage for patients.

Last, treatment with valrubicin is safe. There is no increased risk of progression while salvage therapy with

the agent is attempted.

[Slide]

Valrubicin was patented in 1977. Anthra filed its IND in 1991. Orphan drug status was obtained in May of 1994, and the NDA was filed in 1997.

[Slide]

Valrubicin is the product of anthracycline research program, sponsored by the NCI and undertaken at the Dana Faber Cancer Center by Drs. Mervin, Israel and Emile Frye. Research continues to this day at the University of Tennessee Medical School.

[Slide]

It is a semi-synthetic analog of doxorubicin, differentiated by two key substitutions. On the 14 carbon position of valrubicin we have a valerate group not present on doxorubicin, and on the glycosidic amine unsubstituted with doxorubicin there is a trifluoroacetyl group. These structural modifications render the molecule highly lipophilic and result in important pharmacologic differences between the two agents.

[Slide]

Unlike doxorubicin, valrubicin traverses cell membranes and penetrates into cells rapidly. This slide demonstrates the uptake of both valrubicin and doxorubicin in squamous carcinoma cells incubated over 4 hours with the

drug. As you can see, uptake of valrubicin is much more rapid than with doxorubicin. This finding has been replicated in similar studies using leukemia cells lines, with quantitative HPLC methodology.

Once inside the cell, unlike doxorubicin and other anthracyclines, valrubicin does not associate with negatively charged membranes. We believe that this is responsible for the reduced contact toxicity seen with valrubicin.

[Slide]

Both valrubicin and doxorubicin have been evaluated against a variety of bladder cancer cell lines, including three derived from patients with invasive high grade tumors, exhibiting mutations and p16 methylation, RB and p53, known genetic abnormalities in patients with aggressive disease. This work in particular was done by Drs. Resnikoff and Swaminathan at the University of Wisconsin.

[Slide]

Doxorubicin is a vesicant and, as such, is associated with significant contact toxicity. As you all know, there is no more dramatic illustration of this type of contact toxicity than the sequelae following paravenous extravasation where severe local injection site reactions occur and oftentimes ulceration.

One of the things that impressed the early researchers the most about valrubicin was that upon inadvertent paravenous extravasation there were no severe local injection site reactions, and no ulceration. This led the early researchers to begin thinking of valrubicin for local regional administration, and has dictated the direction of development of this drug till today.

When we took over the product as a company, we commissioned Redfield Laboratory to perform a couple of studies looking at the contact safety of this drug, both in rabbits, one a dermal model and an ocular model. In the dermal model valrubicin was shown to be non-irritating, and in the ocular model mildly irritating but if the eye were flushed with saline non-irritating.

[Slide]

Intravesical pharmacology and toxicology studies in rats and dogs were performed. The results indicate minimal systemic exposure, as documented by extensive recovery of the drug from the urine, and detection of low anthracycline levels in the blood, and insignificant histopathology findings in the bladder and distant organs.

[Slide]

In summary, on the basis of the lipophilicity, cellular penetration, cytotoxicity against aggressive bladder cancer cell lines, contact safety, lack of system

absorption and local regional tolerability in animals, valrubicin was further studied in the clinic, with clinical trials beginning in 1992.

Before talking about the clinical studies in depth this morning, I would like to invite Dr. Samuel Cohen and Dr. Barton Grossman to come up and say a few words about carcinoma in situ -- three things in particular, the definition of this condition; definition of BCG-refractory disease; and the treatment of patients with BCG-refractory carcinoma in situ.

Carcinoma in situ

DR. COHEN: Thank you, Joe.

[Slide]

I would like to discuss the pathology of bladder cancer today, particularly regarding the pathology and biology of this entity.

[Slide]

In actuality, bladder cancer is two diseases. Although these two diseases both occur in the same patient, they are two different and distinct diseases. One does not lead to the other necessarily. They have very different pathology, biology, clinical behavior and, more recently, demonstrable differences in the molecular biology of this. They involve different genes.

This has been a particularly difficult issue to

deal with in the area of superficial bladder cancer. In fact, in the original Marshall staging classification, these were actually lumped together. They are very different and have to be handled differently.

[Slide]

The low grade papillary tumors are well-known and are by far and away the most common, accounting for about 80% to 90% of all bladder tumors. They are mostly a problem because of their frequent recurrences. The recurrences are usually frequent, multiple, and about 70% or 80% of the patients with this entity will have a recurrence within 5 years. When they do recur, or if there are simultaneous tumors at presentation, the tumors can be either of the same clone or multiple clones. They are not necessarily one continuous tumor. These tumors do not invade the muscle. They do not metastasize. They involve an abnormality on chromosome number 9, and the difficulty with them is with recurrence. The main implication of that is that 10% to 20% of these patients will eventually develop the other bladder cancer disease, which is carcinoma in situ, which is what we are dealing with in today's presentation.

Now, this distinction between low grade papillary tumors not leading to CIS and CIS being a different disease has actually been against the dogma for many years, but this distinction has been led primarily by investigators at

Memorial, starting back in the '50s and '60s, continuing till today, led by such individuals as Leo Koss and Mike Malamed in pathology and Whit Whitmore in urology.

Recently, there was a panel of pathologists, convened by WHO, to discuss this entire issue, and they came up with the suggestion that these papillary tumors are actually not bladder cancers but they were going to classify them as bladder tumors with borderline malignant potential. It is interesting that with a swipe of a pen we can eliminate 80% of bladder cancer in the United States.

The main thing to keep in mind with these tumors is that they are not an indication for cystectomy. They are low grade lesions. They are a problem because they recur and they can cause bleeding but they can be treated by local treatment, TUR or sometimes intravesical therapy as well, but TUR is a perfectly adequate treatment for these.

The other is that there are numerous indicators for these lesions as to probability of recurrence. One is size of tumor at initial presentation; the multiplicity of tumors; the grade of the lesions. Then, the difficulty is in assessing the possible progression, which is related to the 10% or 20% of these patients that will have carcinoma in situ as well.

[Slide]

The high grade lesion is quite different. This

lesion tends to have a high propensity for invasion and ultimately metastasis. This is a lethal disease. It is high grade from the beginning and, in contrast to the chromosome 9 abnormalities of the papillary tumors, these involve p53 gene abnormalities. It also looks like other genes such as retinal blastoma, p16 and some others also involved with this high grade lesion.

The recurrences, whether multiple biopsy sites at the time of presentation or ultimate tumor development after complete responses with BCG, are almost always with the same clone. This is true whether the recurrence occurs in the upper tract in the bladder or in the prostatic urethra, clearly indicating that this is a widespread urothelial type of lesion.

In contrast to the papillary lesions, here size and multiplicity are not very good predictors of either progression or of recurrence. So, the biology is very different.

The other thing is that treatment with just simple TUR is truly not an appropriate treatment for these diseases as that will nearly always lead to recurrence of the disease. In fact, the recent report review by Dr. Herr has indicated that following these patients for up to 10 years, they virtually all will recur if treated simply with TUR.

The difficulty in managing these patients is that

many of them are really candidates for cystectomy, if not all of them, but a few of them will have indolent disease, if they are followed for a period of time, that will not progress. The problem is that we cannot distinguish between the few patients with indolent disease and the multiple patients with progressive disease.

[Slide]

Now, just to address specifically the pathology and the cytology of these lesions, this is a picture of a low grade papillary carcinoma of the bladder. You can see that all the nuclei are relatively uniform. There is lots of cytoplasm, and there are very few, if any, mitoses.

[Slide]

In contrast, carcinoma in situ is a quite different lesion. This is a patient who has papillary carcinoma on the right, here. You can see the very small cells in comparison to the very distinctive carcinoma in situ that we have present here. It doesn't take a pathologist to actually distinguish that this patient has two different entities going on here, and this one is considerably worse looking than the more bland looking lesions, over here.

This is reflected in the cytology that can be done in these patients. Patients with papillary low grade tumors, such as up here, have essentially normal appearing

cytology, and it makes the cytology in these patients not very useful in the detection of these tumors. In contrast, you have cells such as this in patients with carcinoma in situ. These are readily detected, and are present at a greater incidence in patients if it is done with bladder washings rather than urine specimens. The key though is that if these are in the specimen that is examined, there is a very low rate of false-positivity. If they have these cells somewhere in the urinary tract they do have CIS. The problem is that there is a variable number of false-negatives, and this comes into play in following these patients either in the beginning or during their course, and the rate of false-negatives can be anywhere from about 10% up to as high as 50% or 60%. So, this is a problem in the management of this, and it is reflective of the type of collection procedures done with these, as well as the expertise involved in the processing and reading of the slides.

[Slide]

The company has asked me to address specifically some questions regarding the entity of carcinoma in situ but, first, I would like to just briefly summarize.

That is, carcinoma in situ is anaplastic lesion that involves the entire urothelium. The diagnosis is established by biopsy, not by cytology. Cytology just tells

you that you had better look really hard for the presence of the lesion somewhere in the urinary tract.

It has a very high potential for invasion and progression, in contrast to low grade tumors.

It requires aggressive treatment of the entire bladder urothelium, which is why the treatment is never localized treatment, such as TUR. It is either cystectomy or, now that we have it available, BCG or, hopefully, some additional chemotherapeutic agents such as the drug under consideration.

[Slide]

The first question is what constitutes Tis? I think I have explained that fairly straight forwardly, but it is a disease that generally involves the entire urothelium although you may only see specific lesions in certain parts of the bladder. But, clearly, clinically it has become the experience or urologists over the years that you have to consider the entire urothelium at risk, which is why the treatment has been either cystectomy or intravesical therapy that can expose the entire urothelium to treatment.

Also, there are tumors that do recur with carcinoma in situ or, if they progress, are the same clone as the initial tumor. Also, the molecular changes that are present are the same in the initial lesion as well as the

subsequent lesions, and if you biopsy the areas of normal appearing epithelium in patients with CIS, the histologically normal-appearing epithelium, they will very often have the molecular changes that are characteristic of CIS already, even though they don't show the disease at that time.

The second question is did the patients entering the primary efficacy studies have diffuse Tis? I think one could argue that at initial presentation there may be exceptional patients that have very localized Tis or carcinoma in situ. These patients, in this study, are at least on their third recurrence of the disease. It is very clear that they have disease that is beyond the size of a biopsy because they have not had the recurrence of the disease well documented with pathologic biopsy.

[Slide]

The next question is does TURB/fulguration or biopsy alone adequate or appropriate treatment for this disease? For newly diagnosed carcinoma in situ, one might be able to make the argument, but I think given the success of BCG it would be highly unlikely that you would rely simply on TUR for the treatment of this disease under any circumstances, although there may be a patient or two that will refuse the BCG and then you can treat with TUR and follow them.

However, in patients that are BCG-refractory, such as the patients under consideration, TUR is clearly not an appropriate treatment. These patients have clearly shown they have extensive disease that is not going to be controlled simply by a biopsy or by TUR. They have already recurred now at least twice, and they need more extensive treatment. I think treatment with TUR at this point, unless it is simply the only treatment that the patient will allow, would be considered negligent medical practice.

[Slide]

Lastly, does the number of biopsies in which Tis is present affect the decision to administer intravesical therapy or perform cystectomy in patients, firstly, with newly diagnosed carcinoma in situ? There is some evidence in the literature that if a single site biopsy is positive at the initial diagnosis, the potential for progression and even the time to recurrence will be less than if there are multiple sites positive. There are some other studies that don't support this conclusion. But, clearly, now when we have patients with a third recurrence, first of all, there is no data in the literature that studied such a group, but data even from the current group of patients would suggest that these patients, since they have extensive disease, and no longer even possibly localized disease, whether they have one site positive or multiple sites positive their chances

of response to the drug, complete response or non-complete response to the drug, does not matter whether one site was positive or multiple sites were positive.

That is all I really have to say at this time. Thank you.

Bladder Carcinoma in situ

DR. GROSSMAN: Good morning.

[Slide]

My name is Bart Grossman, and what I am going to do this morning is talk a little bit about carcinoma in situ in the management and issues in 1998.

[Slide]

As you know, bladder cancer is the fifth most common non-cutaneous malignancy in man, with over 50,000 new cases annually and over 11,000 deaths each year. It most commonly presents as localized disease, and there is a race difference in the prevalence of localized disease, favoring that of the white American population as opposed to the African American population. Fiver-year survival is related both to the stage and also to race. These two variables are not unique to bladder cancer but are commonly seen in other neoplasms in the United States.

[Slide]

As Dr. Cohen stated, it is now well-recognized, both from clinical grounds and through molecular techniques

that there are two pathways to the development of cancer. The more common pathway is that of the non-invasive papillary tumor which is rarely associated with progression to invasive disease. The less common pathway is that of carcinoma in situ, common associated with alterations in the p53 tumor-suppressor gene, and these appears to be, by all available evidence, the predominant pathway to development of tumor invasion.

In 1998, several facts are now well recognized: Carcinoma in situ is transurethral. It is diffuse disease. The diagnosis is made by biopsy. Transurethral resection is not effective therapy, and cytologic findings do not dictate treatment.

[Slide]

What I would like to do this morning is to discuss the fact that BCG is the treatment of choice for carcinoma in situ; that BCG-refractory carcinoma in situ is an important problem in the United States; that cystectomy is the current way that this is usually managed; and that there is a compelling need for alternatives to cystectomy in the treatment of BCG-refractory carcinoma in situ.

[Slide]

The treatment of carcinoma in situ has evolved with time. Over 20 years ago, when Riddle published his historical paper, carcinoma in situ was under-diagnosed and

the only treatment at that time was cystectomy. There were no other treatment alternatives.

[Slide]

In 1982, the Southwest Oncology Group embarked on a major clinical trial, which has since been published in The New England Journal of Medicine. There were 285 individuals enrolled in this trial. The eligibility was patients with recurrent Ta or T1 disease or carcinoma in situ and, importantly, stratification was by the presence of carcinoma in situ.

[Slide]

Now, the treatment in this trial was BCG and doxorubicin. If we look at the overall Kaplan-Meier plots for time to recurrence, you see that the patients who received BCG and had carcinoma in situ did dramatically better than the patients who received doxorubicin and had carcinoma in situ. The patients who had only papillary disease, again, had a better response with BCG than doxorubicin, although the curves are somewhat closer together. Both of these differences are statistically significant. At this point in 1998, doxorubicin is rarely used for the treatment of papillary disease and is not used for the treatment of carcinoma in situ.

[Slide]

The Southwest Oncology Group then embarked on

another trial, evaluating the role of maintenance BCG. In this trial, 550 patients were enrolled. Patients had, again, either recurrent papillary disease or T1 disease or carcinoma in situ and, again, there was stratification for the presence of carcinoma in situ.

[Slide]

These also are Kaplan-Meier plots for time to recurrence. The patients with maintenance therapy are shown in yellow. The patients who received only an induction course are shown in white. Interestingly enough, the curves are now reversed. The patients who had papillary and T1 disease are the solid lines, and here the difference is more dramatic than for patients who had carcinoma in situ, the dotted lines. Nevertheless, there are statistically significant differences between both groups. However, it suggests that maintenance therapy is particularly effective in patients who have papillary disease.

[Slide]

But there is a price to pay for maintenance therapy. This table shows that of patients who had only a 6-week induction course of BCG, approximately 40% of patients remained free of symptoms. Patients who received maintenance therapy, only 21% of patients were free of toxicity. In virtually all of the classifications looked at, the overall incidence of toxicity doubled with

maintenance therapy. In fact, many patients could not complete their 3-year course of therapy due to intervening toxicity.

[Slide]

This is data from Washington University. It shows the long-term results with BCG in patients receiving 1 or 2 courses of intravesical BCG. These are induction courses. It shows that despite the fact that BCG is very effective for treating both papillary disease and carcinoma in situ, there is a significant incidence of long-term treatment failures. These curves steadily deteriorate over time. So, BCG-refractory disease is going to become an increasing clinical problem in the United States.

[Slide]

So if we take a historical look of carcinoma in situ and come to the present, the initial treatment for carcinoma in situ was cystectomy. With the advent of the major trials through the Southwest Oncology Group and other trials also showing similar data, BCG is now considered the standard.

What has occurred is that BCG-refractory disease is now a new problem, and cystectomy is a treatment of choice for BCG-refractory disease. The current problem that we are now facing in 1998 is a consideration of salvage intravesical chemotherapy as a possible alternative to

cystectomy in BCG-refractory disease.

[Slide]

So, the question now is what is BCG-refractory carcinoma in situ? Clearly, patients who have received two induction courses of BCG have BCG-refractory disease. Those individuals who have received the 6-week induction and particularly the maintenance course that has been used in the Southwest Oncology Group, which is a series of 3 weekly mini-inductions, should be considered BCG-refractory. Finally, patients who have had BCG treatment limited by toxicity have obviously received the maximum treatment that they can receive.

[Slide]

So, what is the therapeutic strategy in BCG-refractory disease? Well, one obvious strategy is giving more BCG. As I will show you in a minute, this now results in a change in the risk/benefit ratio favoring increased risk. Furthermore, there is significant increased toxicity, as shown in the BCG maintenance trial which was conducted through the Southwest Oncology Group. Radiotherapy is not an option for BCG-refractory disease, and has never been shown to be active in the treatment of carcinoma in situ. And, obviously we are here to discuss second-line chemotherapy in the treatment of this disease.

[Slide]

This is data again from Washington University, showing that the additional courses of BCG after induction and a second course become associated with increased risk.

[Slide]

This data is shown on this slide. It shows that in patients who have failed two courses of BCG and get additional BCG the proportion of patients becoming tumor-free decreases; the proportion of patients having invasive cancer increases; and the proportion of patients having metastatic disease increases. So, the risk/benefit ratio does not warrant a third induction course of BCG.

[Slide]

What then are the other alternatives, given information in the literature, and admittedly there is very, very little available data? This is a randomized trial with a crossover to mitomycin, published by Lundholm. There were 14 patients. There was 1 complete response in patients who failed BCG therapy, for an overall 7% complete response rate.

For interferon, Glashan published 2/9 patients who had failed BCG, who had a complete response rate at 3 months, and the response rates were very short, ranging from 5.8 to 11 months.

Dick Williams published in an abstract that 10/20 patients achieved a complete response at 4 months, however,

the responses were not durable and lasted less than 6 months.

Because of the low response rates with these drugs, they do not appear to be suitable candidates for a Phase III trial in a BCG-refractory carcinoma in situ setting.

[Slide]

Some time ago Dr. Whitmore said that radical cystectomy may be the gold standard but don't cast it in bronze.

[Slide]

Radical cystectomy is associated with a mortality of 2% to 3%, early morbidity of approximately 30% and a late morbidity of approximately 30%.

[Slide]

And, it is associated with decrease in quality of life, impotence and urinary diversion of some sort. The ileal conduit used to be the standard. Increasingly, continent pouches and neobladders are being performed. Nevertheless, neobladders do not function as well as the natural bladders that you and I were born with.

[Slide]

What are the alternatives that can occur if patients are treated with salvage therapy for BCG-refractory carcinoma in situ? If patients fail with carcinoma in situ

or worse disease, then they should probably go on to cystectomy. The real winners, of course, are the patients who are rendered free of disease, have their bladders and are doing very well.

But there is another very interesting group, and those are the patients who recur with papillary disease only. In this group, it can be argued that these patients have had eradication of their malignant clones and are left with a much more benign disease. These people can, in fact, maintain their bladders and are then amenable to other forms of local therapy, and these patients have definitely received benefit from this salvage therapy.

[Slide]

So in conclusion, carcinoma in situ is an aggressive disease. BCG is the primary treatment for this. BCG-refractory disease is an increasing problem. Cystectomy is the principal therapeutic option for patients with BCG-refractory disease, but alternative treatments are desperately needed.

[Slide]

The company has asked me to address several questions. First, were the patients enrolled in the primary efficacy studies, A9301 and A9302, candidates for immediate cystectomy at study entry? There is no doubt in my mind this is true. They failed BCG. This is a very heavily

pretreated population with recurrent carcinoma in situ, and the current standard is radical cystectomy in this population.

Then, the real question is are they candidates for immediate cystectomy upon documented clinical failure? And, the answer to that is both yes and no. It depends upon how they failed. Patients who failed with only papillary disease or patients who failed by virtue of two positive cytologies, these are not patients who I would bring to cystectomy.

[Slide]

Second, are the results of cytology a deciding factor in determining whether a patient with pathologically confirmed carcinoma in situ of the bladder is a candidate for cystectomy or intravesical therapy? The answer to this is a categorical no. I do not base therapy on cytology results.

[Slide]

Three, based on the natural history of BCG-refractory carcinoma in situ, do the following findings suggest to you that treatment with valrubicin may have put patients at increased risk for the development of pathologically advanced disease, metastases, and death? And, 3/37 patients had pT3 disease or greater; 4 patients died of bladder cancer. Of the patients with advanced

disease, these were well within the clinical range of under-staging, a fact that Dr. Gulfo will discuss later. In a session tomorrow at the American Urologic Association meeting in San Diego, which I will be moderating, data from Memorial Sloan-Kettering Cancer Center shows that carcinoma in situ is associated with a 38% under-staging rate.

Four patients did die of bladder cancer without ever going to cystectomy and, since they did not go to cystectomy, you cannot assume that valrubicin delayed their ability to cystectomy. In fact, most patients are offered cystectomy and, as you have heard earlier, there is a significant reluctance on the part of many individuals to undergo this procedure even though it is potentially life-saving.

[Slide]

The last question, based on the data collected from the patients in the primary efficacy studies, A9301 and A9302, how many patients had complete response? From a personal and careful review of the data, I am convinced that there are 15 patients who did have a complete response and would be considered a complete response in any series in the literature. Thank you.

Valrubicin Clinical Data

DR. GULFO: Thank you, Drs. Cohen and Grossman.

[Slide]

I would like now to take the rest of the time discussing the clinical data of valrubicin intravesical administration.

[Slides]

The NDA program consisted of 6 clinical studies in which 230 patients received at least 1 dose of valrubicin. The primary efficacy studies were A9301 and A9302, and I will discuss those in depth in a moment but let's talk about the highlights of the major findings of those studies.

A991-01 was the first study ever conducting in patient intravesical administration. It established the 800 mg dose as the maximum dose, and the dose we took for further study. Local bio-symptoms with the dose-limiting toxicity and activity in patients previously exposed to BCG was documented. Two of seven patients with carcinoma in situ had responses for over 2 years, and both of those patients had failed prior BCG and thiotepa.

A9501 was the first study we ever performed perioperatively, administering the drug within 1 hour of a TURB for patients with papillary tumors. This study also documented the safety of an 800 mg intravesical dose with valrubicin.

A9303 was a supportive safety study, conducted in parallel with these studies, in 80 patients with carcinoma in situ, and the major finding in this study was that

patients receiving 7 or more doses of the drug had a greater number of treatment terminations than patients receiving 6 or less doses. A9305 I will discuss presently with respect to pharmacokinetics.

[Slide]

Three parameters were assessed in pharmacokinetic analyses, systemic exposure, urine recovery and absorption/ distribution in the bladder wall. Data from 50 patients from 6 clinical studies were analyzed.

[Slide]

This slide demonstrates the area under the curve calculations for systemic exposure following an intravesical or intravenous administration of valrubicin. Intravesical administration results in negligible systemic exposure, especially when compared with the intravenous. Note that after intravenous administration of this drug, 75% of patients developed grade 3 or grade 4 myelosuppression, and we saw absolutely no myelosuppression in patients receiving therapeutic or prophylactic courses of intravesical therapy.

[Slide]

This slide demonstrates the recovery of anthracycline species from the urine. Note that after an intravesical dose nearly all drug is recovered, and virtually all of it as parent unmetabolized drug.

[Slide]

This slide illustrates the concentration of anthracyclines in 3 areas of the bladder, dome, left and right walls, as a function of distance from the luminal surface. Shown in the bar are the IC-50 concentrations of the aggressive cancer cell lines I showed a few slides back. Absorption through the bladder wall, as you can see, did not vary by site within the bladder, and at the depth of a submucosal tumor, T1 tumor, 3 times IC-50 concentrations were observed.

[Slide]

I would now like to focus on the primary efficacy studies, and I will discuss effectiveness first. There were 2 studies conducted, A9301 and A9302. They were exactly the same, with the exact same inclusion criteria, the exact same procedures, the exact same protocols -- just conducted at different clinical sites.

It was agreed with the Agency that the 2 studies would be pooled and presented in 1 study report in order to provide more meaningful estimates of various efficacy and safety parameters. The design was open label, where 800 mg of drug was administered, held for 2 hours, voided by the patient. That was to be done on 6 consecutive weeks. A total of 90 patients was enrolled.

[Slide]

In order to be eligible for this study, patients had to have pathologically proven carcinoma in situ of the bladder. They also needed to have been treated twice in the past prior to study entry for treatment of carcinoma in situ, and at least 1 of those treatments had to have been BCG. So, what we have at presentation of the study, the patients entered having carcinoma in situ diagnosed on 3 separate occasions, twice in the past when it was treated and once at baseline for which valrubicin treatment was to be administered.

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The median age of the 90 patients was 69.5. Males outnumbered females 7 to 1. There were only 2 non-Caucasian patients. The median duration of disease from initial diagnosis of any form of superficial bladder cancer to study entry was 3.3 years. Recall, in that period patients had to have carcinoma in situ 3 times.

[Slide]

This slide summarizes the prior treatments the patients received. All patients received at least 1 course of therapy. All but 1 patient received the protocol-specified 2 prior intravesical regimens. And, 100% of the patients, as per protocol, received 1 prior induction round of BCG -- a round is 6 cycles. and, 70% of the patients received 2 induction courses of BCG. Looking at prior

TURBs, 82% of the patients received at least 4 prior TURBs.

[Slide]

This slide demonstrates the time to failure from the most recent BCG that was received by the patients prior to study entry. As you can see, the patients had a most inadequate response to prior BCG treatment. It is a little more apparent when we compare it to some data that Dr. Grossman showed previously from Nader and colleagues.

Looking at this, the time to failure following 1 or 2 courses of BCG, the median time is 5 years versus the patients entering our study where the median time is 9 months. These patients clearly had BCG-refractory carcinoma in situ and, as such, were candidates for immediate radical cystectomy.

To dramatize that point further, let's skip ahead to what happened after valrubicin treatment. Of the 60 patients who failed with carcinoma in situ after valrubicin, 37 went to cystectomy. That is 62%. This is clearly a pre-cystectomy population.

What expectations can we have about valrubicin's performance in this most refractory setting, at least third-line setting, and many times it was fourth and fifth? Well, clearly expecting front-line response rates of 50% and greater we do not believe is rational. In discussing the

project with FDA over the years, I think two things came out in all of our discussions. One is that duration of response is critical, and the other is that an evaluation of the risk of developing pathologically advanced disease while salvage treatment was attempted would also be critical.

[Slide]

The patients were to be followed by cystoscopy, biology and cytology. This was performed at baseline, then after 6 weeks of treatment, performed again at 6 weeks or at 3 months from baseline, and then at 3-month intervals or until failure. Cystoscopy every 3 months, with biopsy of suspicious lesions seen on any cystoscopic examination. Biopsy was to be performed at 3, 6, 12 months and annually thereafter. Failure was defined as the first evaluation at which biopsy-proven superficial bladder cancer was documented.

[Slide]

Consistent with other studies of carcinoma in situ, notably Southwest Oncology studies, a single positive cytology did not constitute failure. As stated in the protocol, in order for cytology to be used as a sole basis for failure 2 successive positive cytologies had to be documented.

[Slide]

In patients in whom failure occurred, long-term

follow-up at 6-month intervals or until death for disease status was conducted, and this was done predominantly via chart reviews and telephone contacts with referring physicians and patients.

[Slide]

Complete response was defined conservatively. In order to be designated a complete response in this study, patients had to be disease-free both at 3 months and at 6 months. Because cystectomy is the principal therapy for patients with BCG-refractory carcinoma in situ, the investigators wanted to be extremely conservative and cautious before labeling any patient a complete responder.

[Slide]

This slide depicts the response rate at various time points following valrubicin treatment. At 3 months, the traditional time point in studies of carcinoma in situ where "complete response" is declared, we saw a 44% response rate. The complete response rate was 19/90 or 21%. Now, recall that for this study, given the fact that cystectomy is the principal therapy, we defined complete response at 6 months. Why? Because we didn't want patients that had other than a robust response having the risk of having a cystectomy delayed. The median time to failure or last follow-up in the complete responders was 18-plus months.

[Slide]

This slide demonstrates the complete responders, with the Anthra number here and the FDA number here to facilitate your review. Now, 19 patients had met the criteria for complete response as established in the prospective design of the protocol. The Agency reviewers considered 14 patients as complete responders, with these 7 having a less extensive documentation of response than these 7, and the Agency considered these 5 patients not to have had a complete response.

[Slide]

In an effort to try to achieve consensus with the Agency, we reviewed our complete responders with our advisors, investigators and our experts. There was unanimous agreement that unequivocal complete responses were seen, as Dr. Grossman stated, in these 15 patients. These 15 patients had significant clinical benefit following valrubicin treatment and, furthermore, would be considered complete responders in any series of carcinoma in situ. Now, looking at the protocol criteria, we believe that all patients were complete responders, and I would be happy to entertain any questions regarding these 4 patients. But even if we were to omit them, this does not change the stated response profile of this drug critically.

[Slide]

What I would like to do now briefly is take a look

at two of the principal objections raised by the Agency in their review of the complete responders. The first objection goes like this: carcinoma in situ documented on one biopsy without a positive cytology following the resection procedure, fulguration or biopsy, one connotes disease not requiring aggressive treatment, two, perhaps connotes "unifocal" disease, and all of this leading to the conclusion that biopsy alone may have eradicated the disease.

[Slide]

Now, as Drs. Cohen and Grossman have stated in various ways, carcinoma in situ is a diffuse disease and, unlike papillary tumors, the number of sites positive is irrelevant. It requires treatment of the entire bladder and, as Gils-Gielen has shown, the number of sites documenting Tis, the number of positive biopsy sites has no effect on response to treatment, recurrence,, progression or survival. As numerous authors have shown -- Utz, Whitmore and Herr -- TURB or biopsy alone is simply not adequate treatment for this disease. Now, that is fine in the absolute but we are talking now about patients entering the study having failed two prior regimens, BCG-refractory, and in that group, I would like to say even if an indolent form of carcinoma in situ could ever be documented, this isn't it. These patients have refractory, recurring through the

principal forms of therapy and are immediate cystectomy candidates.

In A9301/02, 47% of the patients had carcinoma in situ documented on 1 biopsy and there was no statistically significant difference in the proportion of responders versus non-responders with 1 positive biopsy.

Now, in discussions with the Agency regarding this issue, at one point it was communicated that, well, if patients somewhere in their past -- if it could be shown that several sites in their bladder were involved, then that might satisfy everybody that it was truly diffuse disease and, indeed, 17 of our 19 patients had a history of multiple sites within the bladder, biopsy-proven, diagnosing the disease.

[Slide]

What about the cytology part of this argument? Well, as Dr. Grossman stated, positive cytology alone does not dictate management. In fact, as Badalament and associates have shown at Memorial, when you have positive biopsy of carcinoma in situ and you are using voided urine, up to 61% of patients can have a negative cytology. Now, in our series 34% of patients had a negative cytology, and there was no statistically significant difference in the proportion of responders and non-responders.

[Slide]

The second objection that I would like to talk about is this, in order to prove complete response, biopsy of the areas at which carcinoma in situ was diagnosed at baseline is required in follow-up.

[Slide]

Now, again as Dr. Cohen and Dr. Grossman stated, Tis is a diffuse disease; it is not focal, and it cannot be evaluated on a per lesion basis. It requires evaluation of the entire bladder urothelium, and that is done via cystoscopy, with biopsy of suspicious or preselected areas, as the standard of care. As Kiemeney has shown, biopsy of cystoscopically normal appearing areas has added little and is not part of good medical practice.

Now, what about our studies? Well, there are 2 patients that had biopsy-proven carcinoma in situ at 1 site at baseline and failed with biopsy-proven carcinoma in situ at another site. In 11 of those 12, the site positive at baseline by biopsy was negative at failure by biopsy, and the site positive at failure by biopsy was negative by biopsy at baseline. I think this demonstrates that simply biopsying the site involved at baseline does not do this disease justice and shouldn't be the basis upon which complete responders are based.

[Slide]

Let's take a look at a patient in whom both

objections were raised. This is a 76-year old white male, with initial diagnosis of transitional cell carcinoma in '87, treated with mitomycin in '89. Prior treatments for carcinoma in situ included 3 rounds of BCG, 1 in 1991, 1 in 1993, 1 in 1995, and then immediate treatment thereafter with interferon which also did not control the disease. The patient presented with carcinoma in situ, was treated for 6 weeks, had multiple cystoscopic evaluations, multiple biopsy procedures as per protocol, and multiple cytologic assessments in follow-up.

Now, when we met with the Agency for our pre-filing meeting in August of 1997, the Agency asked us to split out this biopsy column. They wanted to see the different sites within the bladder where biopsies were preformed in the history as well as in follow-up. So, if we do that the slide gets a little busy.

[Slide]

We have posterior wall, right wall, left wall, left ureter, the neck posterior -- I don't even know -- anterior wall, trigone, dome -- okay, let's go on. Anyway, it is obvious that the patient had multiple sites of Tis in the past, carcinoma in situ at baseline, many, many biopsies in follow-up, cytology evaluations, all negative.

As can be seen, the documentation of complete response in this patient is most adequate and, as Dr.

Grossman stated, this patient would be considered a complete responder in any series of carcinoma in situ.

[Slide]

Let's take a look at outcomes. The median follow-up of the entire population was 23 months, ranging from 1 to 44 months. The Agency instructed us not to file the NDA until we had 50% of patients followed from the initial evaluation followed for a year. We actually filed with 70% followed for a year, and the median time from that first disease evaluation was 19 months. Four patients were lost to follow-up. So, looking at clinical stages at baseline and failure, it is 79 patients; 7 are still disease free, so no recurrence there, and 4 lost to follow-up. At baseline we see 74 patients had carcinoma in situ with or without a Ta tumor. The breakdown was 63 with carcinoma in situ alone, 11 with Ta in combination with carcinoma in situ, and 5 with Tis and T1 disease. Then at failure, you see the range of the breakdown. It is very similar.

If we look here, 2/79, or 2.5%, had clinical progression, that is, development of a T2 tumor: 1 patient had T2 in conjunction with carcinoma in situ and the other patient had T2 alone. The patient with T2 in combination with carcinoma in situ went on to cystectomy and at cystectomy had pathologically T2, Tis disease.

[Slide]

I am now ready to speak about safety. A total of 230 patients, as stated previously, received at least 1 dose of valrubicin. Now, 170 of them received it in a manner most consistent with the labeling that we have included in the filing. That is, multiple cycles of 800 mg doses. So, I will focus most of my discussion on this group but we will talk about deaths and serious adverse events derived from the entire data base.

[Slide]

This slide depicts the adverse events that occurred in greater than 5% of patients. As you can see, the principal toxicity of this drug is local bladder symptoms, occurring in 88% of the patients, the others in 5%. Two-thirds of these events are grade 1 or grade 2; 90% of the events in these categories are grade 1 or grade 2.

[Slide]

Well, since local bladder symptoms is the most common event, let's take a little closer look at it. This slide demonstrates the frequency and severity of local bladder symptoms at baseline, during the treatment period and then after the treatment period. As you can see, 45% of patients entered the study with symptoms; 88%, as I just showed, developed symptoms during treatment; and 51% had symptoms at the end of treatment.

So what we conclude from this is that frequency

and severity -- severity increases during treatment -- incidence and severity of adverse events of local bladder symptoms is reversible. Most of these symptoms were transient and reversible.

[Slide]

What about serious adverse events using the entire safety data base? We see that the investigators considered 3 events drug related. Let's talk about them. One was reflux nephropathy in a patient shown to have reflux nephropathy on prior BCG treatment.

There was a patient with mild contact dermatitis, self-limited, untreated, resolved without any sequelae. The reason the investigator called this into us was we didn't have any investigators for sure up till that time and, by definition, that is a serious adverse event. Now it wouldn't be because we put it in the brochure.

Myelosuppression -- there was 1 patient with an iatrogenic bladder perforation. In that perioperative study the dose of drug was absorbed. He had systemic exposure similar to an intravenous dose. It resolved without sequelae, but did have grade 4 neutropenia. The most striking thing about this patient is that there was no peritonitis.

[Slide]

What about deaths? Of the 230 patients, there

were 32 deaths either during the study or on follow-up,, and 10 patients died of bladder cancer. I would like to take a closer look at those patients.

[Slide]

All 10 patients failed clinically early, either at the 3-month time point or at the 6-month time point. In fact, only 1 of the patients had T2 disease at clinical failure. The time from documented clinical failure to death was over a year in 9 of the patients and in the other it was 8 months, and over 2 years in 3 of the patients. Four of the patients who died, 4/10, went to cystectomy prior to death, and disease was localized, pathologic stage T2 in 2 patients and pathologic stage T3 in 2 patients.

[Slide]

As I said earlier, one of the most important considerations of valrubicin for treatment of patients with BCG-refractory carcinoma in situ is the evaluation of the risk of developing pathologically advanced disease during the salvage treatment. At the start of the study, we and our investigators felt this risk was extremely low given the treatment regimen -- 6 weeks of drug, 6 weeks respite and then immediate disease evaluation where, if failure was documented, the patient and the physician could make an educated decision about what therapy to consider next.

[Slide]

In order to evaluate this risk, we need to look at cystectomy outcomes. Before we do that, we have to define what pathologically advanced disease is. Pagano et al. helps us. He published a series looking at the 5-year survival correlated with stage at cystectomy. What he showed was that patients with pathologic stage T3 disease, the deep layer muscle in the bladder, had much, much poorer outcomes than patients with pathologic stage T2 disease or actually no disease at pathology or Tis or T1.

[Slide]

So, using greater than pathologic stage T3 disease, let's take a look. In the A9301/02 and 03 studies, we have data on 55 patients who underwent cystectomy. They went to cystectomy a median 10 months following the biopsy that got them on the study, documenting Tis. So, 10 months later at their cystectomy, 8 patients, or 15%, had pathologic stage T3 disease.

[Slide]

What does that mean and how does it compare to the literature? Well, Amling and associates published a series looking at cystectomy. In their analysis, they looked at the clinical stage immediately prior to cystectomy comparing it to the pathologic stage at cystectomy. So, the interval here is 10 months; the interval here is virtually immediately. And 220 patients had Ta, T1 or Tis disease.

At cystectomy, 39 or 18% had pathologically advanced disease. Well, this is a common phenomenon where clinical staging immediately prior to cystectomy indicates less advanced disease than stage at cystectomy, and it is called pathologic upstaging. Dr. Grossman used clinical under-staging earlier.

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Why does this happen? Two words -- sampling error. In clinical staging the samples used are based on TURB. Tumors are resected from the bladder and sent to pathology for analysis, whereas in pathologic staging the whole ex vivo bladder specimen is sent. It makes sense then that this type staging will demonstrate more advanced disease than clinical staging.

[Slide]

What can we say then about treatment with valrubicin and the risk of developing pathologically advanced disease? Well, since the incidence of finding pT3 disease or greater at cystectomy in valrubicin failures is about 15%, and the literature-established pathologic upstaging rate is 18%, we conclude that valrubicin certainly confers no significant increased risk of developing pathologically advanced disease.

[Slide]

On the basis of its lipophilicty, cellular

penetration, contact safety, activity against aggressive bladder cancer cell lines, and local tolerability, negligible systemic absorption, valrubicin is a novel anthracycline and ideal intravesical agent for the treatment of patients with carcinoma in situ.

As Drs. Grossman and Cohen have stated, bladder carcinoma in situ is an aggressive disease, requiring aggressive treatment of the entire urothelium; the entire urothelium is at risk. For patients with BCG-refractory carcinoma in situ, cystectomy is the primary therapy. As we have heard today, neither patients nor physicians want to perform cystectomy. Both groups hunger for salvage regimens, but there is nothing approved and, again, no drugs being attempted right now have been shown to be safe or effective.

Valrubicin treatment is effective, inducing complete response in as many as 21% of patients. The responses are durable. The median time to failure is 18-plus months, all of that translating into meaningful salvage for a significant number of patients. Finally, treatment with valrubicin is safe. The local bladder symptoms are transient and reversible, which is the primary toxicity but, most important, there is no significant increase in the risk of progression while attempting valrubicin treatment.

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It is on the basis of this evidence that we seek this Committee's recommendation for approval for the use of valrubicin in the treatment of patient with biopsy-proven carcinoma in situ of the bladder that is refractory to BCG therapy. Thank you.

DR. DUTCHER: Thank you very much. We will now proceed to questions from the Committee for the sponsor. Dr. Scher?

Questions from the Committee

DR. SCHER: Do you have a summary of the time from the initial diagnosis of carcinoma in situ to actual protocol?

DR GULFO: Of carcinoma in situ? I don't know. That was 3.3-year median was from the initial date of any form of superficial bladder cancer.

DR. SCHER: Not Tis?

DR. GULFO: Did we look at Tis? It would probably be less, of course, but I don't know how much less.

DR. DUTCHER: Dr. Sledge?

DR. SLEDGE: I have a question for Dr. Cohen. Do you think pathologically you can define a group of patients who require immediate cystectomy?

DR. COHEN: You mean with the CIS?

DR. SLEDGE: Yes.

DR. COHEN: I don't think so. There are no

definable markers at this point in true CIS. This gets a little cloudy because there has been the whole issue of dysplasia and low grade carcinoma in situ, that sort of thing. But in real carcinoma in situ, high grade, full thickness carcinoma in situ, you really can't distinguish those select patients who are will be relatively indolent versus those who will be very aggressive.

DR. SLEDGE: Now a question for I guess either Dr. Grossman or Dr. Cohen, if that is, indeed, the case, then in the absence of a randomized trial how can one define true clinical benefit?

DR. COHEN: Well, the progression rate is obviously a significant problem, and these patients are at very high risk. The problem is the natural history of the disease continues to evolve. What we can see is that the current standard of therapy is cystectomy. So, that is the treatment, and if you take the bladder out there is no obvious comparison to that and there is no other treatment that has been able to achieve a reasonable complete response rate that is durable. When other drugs have been used, as you can see, either the response rates are very low or, when they are somewhat higher, the duration of response is extremely short.

The fact that the data in this study shows a durable response rate in a proportion of patients is

excellent evidence that the drug is active and is accomplishing something. The other thing that is also evident is that there is an additional proportion of patients which recur with papillary only disease and don't recur with carcinoma in situ, and those patients are left with less malignant disease.

DR. SLEDGE: If I am reading the life-table analysis, on page 170, correctly, there is a plateau at 2 years of about 55%. And, yet, at 2 years there is a continuing CR rate of 10%. Is what we are seeing there a true clinical benefit, in your opinion, or are we just seeing natural history?

DR. GROSSMAN: The natural history of carcinoma in situ in this setting is very bad. They have already demonstrated that they have persistent disease despite multiple therapies. So, one could always argue that there is some baseline natural history but I don't know of any data to objectively support that, and all the data suggests, from the population that was selected for this trial, that you wouldn't expect a proportion of patients to maintain an unmaintained long CR rate spontaneously, yet it did occur. Anything can occur but with the selection criteria used, and the fact that they have aggressively failed other therapies which are demonstrated to be very effective, one would think that that would be extremely unlikely.

DR. SLEDGE: I am sorry, you misunderstood me. I am not talking about the CR rate here, I am talking about the fact that 55% of the patients still have their bladder intact despite the fact that 90% of the patients have failed. Would that occur in your clinic?

DR. GROSSMAN: It would probably not be that high. There are two factors that go into that. One is, obviously, the CRs. The other group of the patients that failed the cytology, the patients who failed with papillary disease, those patients would not have cystectomy in my clinic. The other patients, I would generally recommend that they have cystectomy. Nevertheless, there are some patients who say, "well, what's the next drug you can try? I don't want to have cystectomy." So, there are going to be some of those patients out there. As Dr. Gulfo said, in the patients who are candidates for cystectomy, there was a 50% cystectomy rate, which is pretty high for when you consider that these patients don't even have clinically invasive disease.

DR. GULFO: Dr. Wehle, could you address that? You had two complete responders and you had a number of failures. What happened after the drug failed, and discussions about subsequent therapies?

DR. WEHLE: I think I am just going to say what has already been said. Many of the patients that failed and are faced with cystectomy do not want cystectomy. In our

case, that is one of the reasons why the patients came to us to begin with. They were told they were going to have a cystectomy and we had the study drug to offer them. So, despite that recommendation, I think a large proportion of patients are not going to proceed with cystectomy.

DR. DUTCHER: Just one question, what would be the expected rate of developing papillary carcinoma after any intravesical treatment at this stage of their disease?

DR. GROSSMAN: At this stage, the disease data is essentially completely unknown. The overall response rate for papillary disease for newly diagnosed patients is 50%. For patients who have more aggressive bladder cancer, the recurrence rate at 1 year is 80%. So, in this setting one would expect the recurrent disease rate to be extraordinarily high without effective treatment.

DR. SCHER: Maybe Dr. Grossman can comment on this. It seems to me that trying to use the complete response endpoint is just creating confusion. When you see data graphically illustrating that a patient has developed multiple episodes of Tis in a relatively short time frame, and you see in that same patient, following an intervention, that there is no longer the development of in situ disease, that would appear to me to be much more convincing than trying to debate whether a single site of disease has been resected or not, whether the cytology is positive. Are we

really trying to look at the wrong endpoint by debating whether or not a CR has occurred, and isn't the real issue more of a time to development of new aggressive disease?

DR. GROSSMAN: Yes, the term here is actually pretty foreign to most urologists, and we don't usually use that term. We are looking at recurrence rates in the pattern of tumor recurrence, and I would agree completely. The fact that some patients are rendered free of disease and others are rendered free of carcinoma in situ but recur only with papillary disease is the evidence for a successful result in this population.

DR. MARGOLIN: I have several questions, and maybe Dr. Grossman and also Dr. Cohen will have to help. First of all, in reference to a couple of bullets on slide 48, in which Dr. Grossman, I think, stated emphatically that the patients that were enrolled in these studies were definitely candidates for immediate cystectomy. I don't think there is any question about that, but then a follow-up question of undocumented failure following treatment with AD32, you said that they would be candidates for immediate cystectomy at that point if they failed with diffuse disease, but not based on positive cytology alone or for those lucky patients who ended up with papillary tumors only. So, I am not certain what the criteria would be that you would use to say that then those patients would go to cystectomy.

DR. GROSSMAN: I don't believe I said diffuse disease. If a patient, after treatment, has a single positive biopsy of carcinoma in situ, the treatment of choice in this setting is cystectomy. The patients who are free of disease, obviously, they don't need cystectomy. The patients who recur with papillary disease only, without carcinoma in situ, I would not take those patients to cystectomy unless it was very, very diffuse papillary disease, and I think I have only done two cystectomies in my life for diffuse papillary disease. For patients who fail only with positive cytologies, I don't do cystectomies. Those patients clearly are at high risk. I definitely worry about them. I do lots of biopsies. But the point that they have positive cytologies, you have no idea where the cytology is coming from. So, doing cystectomy just because of a positive cytology is not something that I would normally consider.

DR. MARGOLIN: That was going to be the other question. All of the people who have talked have stressed the diffuseness of this disease. So, I guess the question is does a cystectomy alone do the job, or do you have to find the lesion so that you know whether you have to do cystoureterectomies or nephrectomies, just a little something about the urologic management of this disease?

DR. GROSSMAN: In most cases a cystectomy which

encompasses removing the bladder and the prostate is usually effective. Clearly, in patients who have diffuse disease, they are at increased risk of both ureteral involvement and urethral involvement and we examine that, and sometime ureterectomy is necessary and sometimes further resection of the distal ureteral segments is also required. In fact, in most patients there are reservoirs either in the bladder or the prostatic urethra.

DR. SWAIN: I have a couple of basic questions. Since the drug is not metabolized in the bladder, and a lot of the documentation you have in the book that you gave us stated that topo-2 activity was one of the main mechanisms of action of cytotoxicity and that doesn't occur since you don't have metabolized drug, what is your proposed mechanism of action of the parent drug in the bladder?

DR. GULFO: Well, the drug does get converted to topo intracellularly. It gets converted into a metabolite that does get to top intracellularly. The side chain on the carbon-14 valerate group comes off and then that metabolite with just the trifluoroacetyl inhibits topo. So, that does occur.

DR. SWAIN: Are these highly proliferative lesions pathologically?

DR. COHEN: CIS has a very high proliferative rate.

DR. SWAIN: You had about 26% of patients who had grade 3 bladder symptoms. Were those patients the patients who tended to respond?

DR. GULFO: That is a very interesting question. I don't know, but I can tell you this, in responders there was a higher proportion of patients with symptoms at baseline than in the non-responders. So, we didn't look at that but I wish we did.

DR. WILLIAMS: I have a question about the follow-up of patients who did not get cystectomy. When we asked for the update of the status of patients, the number with metastatic bladder cancer went from 1 to 4, and this came out of a group of people who I don't think were even aware had advanced bladder cancer. So, the question is what is the pool of patients out there who might potentially have advanced cancer that we don't know about, who might be dead at the next update?

DR. GULFO: You want to know what is the potential pool of patients that are still being followed?

DR. WILLIAMS: It has to do with the quality of follow-up of patients who are being treated in some way, who might have metastatic cancer that we don't know about.

DR. GULFO: Well, what we did every six months, the follow-up at that point was that the patients basically went back to their referring physician. What we got every

six months was disease status summary. What that included was intervening therapies, including cystectomy, including systemic chemotherapy. So, we would know by the update we gave you how many patients underwent cystectomy, how many patients were getting chemo as a surrogate for restaging in follow-up. So, what we feel is that a clinical failure these patients should be taken to cystectomy, and we can clearly tell you when that happens. We can clearly look at a clinical upstaging rate. Anything that happens thereafter, yes, we are following the best we can but it is really up to the patient and the physician as to what happens.

DR. ODUJINRIN: How many of the patients received BCG after AD32 therapy?

DR. GULFO: We have that.

[Slide]

This is a summary on those follow-up forms that we received as therapies following failure with valrubicin. So, to answer your question, 18 got BCG only; 2 got BCG and mitomycin. So, a total of 20 patients got BCG after valrubicin.

DR. TEMPLE: I don't know if you need to go back to the slide -- I hate to keep sending you back and forth, but the slide that was up before this showed, if I understand it, three people who had more advanced than

expected disease who didn't have cystectomy, and four people who died of metastatic disease, most of them fairly late. That is out of the 90 in the two trials?

[Slide]

DR. GULFO: This is out of the 90 patients.

DR. TEMPLE: Okay. So, the three with relatively advanced disease have a fairly significant risk of eventually having metastatic disease, although I guess they are not known to have that yet. I mean, I read your five-year survival figures. So, that is at least 7 out of the 90 who went on to have something that either did kill them or may, and at least some of the people aren't followed long enough to know yet whether they are going to develop serious problems. How do you know how this compares with what would have happened if they had had a cystectomy? How can you tell? You must have epidemiologic or some experience that tells you what the cost here is of avoiding immediate cystectomy.

[Slide]

DR. GULFO: If we look at the Amling data and we see that 18% of the patients that had cystectomy over a very long period had relatively advanced disease and, as you said, the 5-year survival after pT3 disease is not very good, so, if you look at our patients, we know that, in fact, 8 of the whole group, 3/37, 3 out of the 102

population, had pathologically advanced disease, and then we throw in those other 4 that, as you said, albeit a long time after, did die of advanced disease, I would like to ask Dr. Grossman what he would expect --

DR. TEMPLE: Just before you do that, the Amling data also refers to people whose grade was relatively low?

DR. GULFO: T1 and Tis.

DR. GROSSMAN: The problem here is that when urologists are looking in the bladder they are seeing the surface, and they can't always see what is below. With obvious large, solid tumors it becomes fairly evident that there is something bad happening below and these people have nasty tumors. But, for some reason, there are some patients with carcinoma in situ that can have a more diffuse infiltrating, progressively very bad disease which, looking at the bladder endoscopically, is not recognizable. It just doesn't look as bad as it is. That is why you come up with a figure of around 18% for really bad disease even when things don't look so bad when you are looking in there, and that is with very experienced urologists.

Now, a solution to that is, why, you could just go ahead and do cystectomy in everybody that has bladder cancer and, in fact, there are a few people who think that is almost a reasonable thing to do, and even they profess it with a little bit of caution. But, the father of urologic

oncology, Dr. Whitmore -- you saw his quote, and both physicians and patients are reluctant to do cystectomy for all patients because if you did that, given the 2% to 3% mortality rate, if you did this in enough patients the cost/benefit ratio would probably shift in the other direction. So, you would actually be hurting more patients than you would be curing. There isn't an easy, simple solution. There is going to be risk on both sides, and we explain the risks to the patients when we talk to them, and most patients who we think have superficial disease really do have superficial disease, but there is always going to be a small proportion of them who have disease worse than we expect.

DR. TEMPLE: Just to be sure I understand though, the Amling data you have there refers to people who had a low stage at the time of cystectomy, and the point is that they too were at risk of having more advanced disease that was not recognized for the reasons that were just given.

DR. GULFO: Yes, exactly.

DR. TEMPLE: So, in answer to the question how much did you pay for deferring your cystectomy, your answer would be, based on this, there isn't any evidence that you had to pay anything. Right?

DR. SCHER: Just to confuse the issue a little more, there are patients who develop metastatic disease

following cystectomy who only had in situ disease.

DR. WILLIAMS: I would like to ask about the point that was discussed. There is a traditional Agency position that it is desirable to have cytology done a day after the biopsy, presumably you could remove the immediate disease and produce an appearance for some time, based on not having pathology or cytology positivity for some time. That is a different issue than whether this is appropriate therapy, which you addressed and, clearly, in these patients that would not be appropriate therapy. But the possibility exists that some patients might be rendered apparently disease free if they only had one lesion and if they had negative cytology. I would just like you to address that possibility, that there are some false-positive CRs produced via this mechanism.

DR. GROSSMAN: Well, cytology has a well-recognized decreased sensitivity. Even for high grade disease the sensitivity of cytology varies dramatically from study to study. Badalament's study showed 39%, 40% positive rates. So, that means you miss 60%. And, that just reflects the nature of the cytology and a whole host of other factors, how it is collected etc. So, a negative cytology doesn't prove that there is cancer. Conversely, a positive cytology, while it has a very high specificity -- the specificity is not 100%, and just because you have a

single positive cytology doesn't prove you have cancer because there is at least one case in the series that had a single positive cytology, and was followed probably another year before five negative cytologies and negative biopsies afterwards. So, why is a single positive cytology positive and the rest negative, I don't have a good explanation. But it is also known that cytology doesn't have 100% specificity. So, you are going to have both false-negatives and false-positive. If it is positive, that is good but cytology doesn't prove that there is carcinoma in situ present, and it doesn't prove where it is. It is a biopsy-proven disease.

DR. WILLIAMS: I don't think you actually answered my question.

DR. GULFO: Yes, if I might try, I think that is being based on some guidelines that you shared with us, and I think it is important to think about those guidelines, written in 1988 and really addressing front-line treatment. In the guidelines, when we look at it, we think that there is an over-abundance associated with papillary tumors, the multifocality and the other type of things. So, I think there is a question there.

The other thing is, I have heard urologists say that if a pathologist tells me that at the base of the tumor there is a little bit of carcinoma in situ, I'm not rushing

to give that patient BCG. I think that is where that comment is coming from, that after a TURB, if the pathologist says, yes, this is the first time, yes, I would want a little more to go on first. But I don't think that that is an appropriate thinking process for where we are at now, if patients have broken through so often.

DR. WILLIAMS: I still think it is an important point, and first-line CIS, yes, it apparently is sometimes adequate treatment for some people with focal disease perhaps. The disease does not come back for some time in some people. The question is, in follow-up, if you have one lesion and you do a TUR, is there some period of time when you don't detect the tumor anymore theoretically or in reality? That is the question.

DR. GULFO: And, I think the answer is just because it is documented on one biopsy does not mean it is a unifocal disease. The second answer is look at the time to failure in these patients. We could look at the prior time to failure in some of those patients, and you will see 4/5 times the treatment with valrubicin is just tremendously -- increased the time to failure.

I would like Dr. Grossman, what do you think we would have seen with TURB alone or the biopsy alone in this group?

DR. GROSSMAN: Yes, I would expect in 6 months you

would see failures in virtually everybody, and when we see patients in the clinic and we get a positive biopsy for carcinoma in situ we don't turn around and say, well, maybe we ought to get a cytology to see if that patient should be treated. There is absolutely no question that these patients should be treated. We use cytology as an indication for diagnosis. If we don't see anything and get a positive cytology, then we know that we need to do some biopsies in areas that we haven't otherwise biopsied. But in patients that have a positive biopsy, we don't need a cytology to confirm that the disease is present. We have already documented that the disease is there.

DR. WILLIAMS: And, you think there is no chance that by TUR, at least for, say, 3 or 6 months, especially 6 months, you might have eliminated evidence of disease by our testing, which consists of multiple biopsies and repeat cytology?

DR. GROSSMAN: Well, I think the one setting where that occurs is the one which Dr. Gulfo mentioned, and that is somebody presenting with papillary disease, and you resect it and there is a little bit of associated carcinoma in situ in the specimens for the first time, and most people wouldn't be real anxious to act on that, and those people do okay -- they are prone to failure but they are not prone to very bad disease in a short time frame. But these are

patients with recurring carcinoma in situ over time that have already failed the best available treatment, and this is a totally different population.

MS. BEAMON: Would you clarify, please, for me an item on the serious adverse events slide? The number of cardiovascular incidents appear a bit high. Would you comment on your finding that these are not drug related?

DR. GULFO: Sure. The median age of the patients was 69.5 years, and all of them had extensive histories of coronary-artery disease.

[Slide]

In fact, if you look at the type of events that occurred, they are basically exacerbations of the coronary-artery disease in follow-up.

DR. LAMBORN: In the materials that we were provided before, on page 147, it notes that in determining sample size you were looking at an alternative hypothesis of a response rate of 30%, which was stated as being efficacy comparable to additional courses of BCG. That would imply that in this population you would expect that if they had been given additional BCG there would have been a 30% response rate. Is that a correct interpretation of that statement?

DR. GULFO: I will address that. This protocol was written by another member of the Southwest Oncology

Group, Ralph Blumenstein, and in working with the Southwest Oncology Group people I have found the only thing they quote are randomized studies. That is it; they do not quote single-center studies.

[Slide]

And, the best data comes from Catalona, where he looked at third-line BCG, and third-line BCG had a 20% complete response rate defined by 3 months. Okay? Defined by 3 months. But the risk of metastasis and invasion was 50%. So, the benefit wasn't worth the risk.

But what Dr. Blumenstein had done, he looked at an early analysis which suggested that further maintenance gives another 30%, divided that by some -- derived that by something that I still can't replicate. We called him last week and he admitted that he had nothing as a target, as an upper limit of what could possibly be expected third-fourth-line. We should take this estimate that he derived for BCG second-line. So, it really is an optimistic upper limit target that really was not based on too much reality. The reality would be the Catalona series, and in this series, before giving 1 BCG the probability of being disease-free was 77%; the probability of invasion and metastasis was 75%. After failing 1 course before the second, the probability of being disease-free is 58%; the probability of invasion and metastasis 11% and 14%. But

after failing 2, which is what we are dealing with now, 20% probability of complete response at 3 months and 30%, 50% respectively for probability of invasive disease and metastasis. So, this is what, if I were a statistician, I would have used to base the target on, but he tried to use swab-derived data in a population that just was not comparable.

DR. LAMBORN: Okay. Two additional questions. One is that you mentioned that a number of patients did go on to get BCG following failure. Do you have information on how those patients did?

DR. GULFO: We don't have information on that, but we can tell you how many went on to cystectomy and how many went on to systemic chemotherapy. But the protocol did not require the follow-ups that happen on study or, indeed, at the study center. These patients went back to their community. So, I do not have any means of even guessing at that, reliable or unreliable data. We just did not collect it.

DR. LAMBORN: The remaining question is, you have an overall statement of time to failure from prior BCG. Can you tell me was there any difference in that duration for those who were ultimately responders in this study?

DR. GULFO: Right. No, the responding groups were very, very similar. Can we go to slides 118 and 119?

[Slide]

We looked at this very, very closely, as you can imagine. If we look at the responders and non-responders, we see median duration of disease prior entry 3.3 years versus 4.4. To answer Dr. Swain's question earlier, based on local bladder symptoms, there was a higher percent in the responders than the non-responders.

[Slide]

When their last BCG was, the timing of failure prior -- no difference there; whether or not positive cytology, history of positive biopsy -- nothing distinguished the non-responders from the responders. And, I think we also did a Kaplan-Meier of responders versus non-responders -- we didn't do that.

DR. MARGOLIN: Before this slide I was going to ask -- I will still ask part of the question, the point was going to be if the trial required only one prior BCG but two prior therapies of any sort, obviously the first question was going to be how many patients actually got two prior BCGs. You have that there. But the question really was going to be, and you can still try to answer it, if only one was required, and let's say you had a group where only one prior BCG was allowed regardless of the other types of intravesical therapy, why a randomized study against a second course of BCG was not initiated for this? It seems

like based, at least on what happened after failure of those patients who had not been extensively pretreated with BCG, that it was still a pretty popular modality to give since two-thirds of your patients went on to cystectomy. So, presumably the repeat BCGs represented a high proportion of those who did not go on to cystectomy immediately, and I think it would be a lot easier to convince this Committee both of comparable efficacy as well as adverse event profile if this were compared with the other most popular approach, which is a second round of BCG.

DR. GULFO: Dr. Grossman, if you like I will say a few things. Seventy percent of the patients, as you said, received two prior BCGs. Can we go back to that slide?

[Slide]

Okay, 30% of patients had 3 to 5 prior BCGs, and I have forgotten the number for the 3 but it was certainly higher than 3 to 5; 40% of patients received prior mitomycin. So, the first question you have to ask is, in the period of time the study was being conducted, 1993 through 1997, what would impel a urologist not to give a second round of BCG because the data on second round BCG are very, very good? So, I would ask Dr. Grossman, what would impel urologists not to give a second round of BCG?

DR. GROSSMAN: Well, there are a couple of reasons. First of all, as mentioned, toxicity because some

people have a significant amount of toxicity and don't want to receive it. The other thing, of course, is you try a drug and it doesn't work and you want to try something else.

The problem is that there are relatively few concrete guidelines in the setting, and that is a problem. The other thing is the further out you get, the less the guidelines. So, it is very obvious, if you have carcinoma in situ everybody knows you should give BCG. That is pretty well accepted. After BCG fails, then it is less clear. Most people think a second course of BCG is probably reasonable given the toxicity, and some people have a fair amount of toxicity. Then, in this setting everybody is basically flying by the seat of their pants, and what is really needed is something that can provide some real guidance to the urologic community saying, well, you have somebody who has aggressive disease and has failed effective therapy, at least you have a reasonable drug to give and if you have recurrent carcinoma in situ after this drug and you have given it your best shot, you had better tell patients cystectomy is absolutely needed because there isn't anything else available. There really is no good algorithm saying what to do in this population.

DR. DUTCHER: Back to Dr. Sledge's question and to this slide though, I mean, if you have people that have had that many prior treatments, isn't that saying something

about those patients in that they keep being able to be retreated? And, where do the responders fall into this group, and are we just seeing a selection of people that are going to respond to whatever you give them?

DR. GROSSMAN: Well, it doesn't tell you that they are responders. It tells you that they have received additional BCG. And, it doesn't tell you how long the responses are. The term that Dr. Scher used earlier I think is really crucial, avoiding things in terms of complete responses is really crucial. What we are doing is looking at recurrence rates. Sure, you can do cystectomy at any point. Cystectomy eliminates your recurrence rate of carcinoma in situ at least in the bladder, but it is associated with some morbidity and mortality. If you give BCG and it fails, and you still get CIS and you give more BCG and it fails -- yes that is possible but the longer you do that, potentially the more dangerous it is going to be, and there is some data from Catalona's group that, in fact, is dangerous and it is very difficult just looking in the bladder and telling for whom it is really going to be dangerous and for whom it is not. So, those figures don't tell you the duration of response, and that tells you the most recent BCG duration of response which is really pretty terrible.

DR. GULFO: Dr. Grossman, if our curve looked like

this, would you not give another course of BCG?

DR. GROSSMAN: In general, I think it is reasonable. The data also suggested that people failing within two years on BCG tend to do much worse and have a higher risk of progressive disease than patients who fail after two years. So, the duration of response or the recurrence rate is a very important issue. If you fail early, you are at higher risk. Patients who fail late would seem to be good candidates for more BCG.

DR. DUTCHER: But do you know where the people that you are saying are responders, that have had these durable responses, fall into these curves and into the numbers of prior treatments? Are they people that have had one or two prior BCGs, or are they people who have had multiple?

DR. GULFO: There is no difference. The response is 70% in 2 prior BCGs and non-responders 70%.

DR. DUTCHER: But you don't know how many prior?

DR. GULFO: We have a list of all of the prior intravesical treatments. There were two today. One patient I think had three BCGs, the other patient had two BCGs.

DR. LAMBORN: As long as you have that slide up there, it is not quite clear to me why you grouped the last BCG 3-24 when you consider that the response durations that we are talking about are within that. I assume that you

have actually looked at it in more detail.

DR. GULFO: No. Dr. Grossman alluded to some data at Sloan-Kettering by Breton where patients who do not have a response of 21.6 months -- this is a single center study, but if you do not get a response of 2 years with BCG, stop therapy; change therapy because the progression rate is very, very high. So, we wanted to look at how many patients failed in that 2-year period, and we thought that was a very, very -- it could have been a significant prognostic sign, and if we had more responders who got their BCG to last beyond 2 years, I would have thought that some of the comments that I have heard today would have been very relevant and cutting.

DR. LAMBORN: Right, but you are now talking about responses that were less than that interval.

DR. GULFO: Right. So, it is well within --

DR. LAMBORN: No, no, I am saying that the responses that you are hoping to achieve with your agent, many of them are less than the 24 months.

DR. GULFO: With defined clinical response at 6 months, I agree, but the other side of it is risk of progression. Catalona's data said 20% of patients with complete response at 3 months. We wanted to see how well this could do without the risk of clinical stage progression, which we saw virtually none of, or pathologic

progression, which we saw very little of compared to the literature.

DR. OZOLS: I think we are all still struggling with the selection and potential benefit. Dr. Cohen mentioned that there is a group of these patients with a different natural history, much more indolent. Is that just retrospectively defined, or how would you separate out the group that have progressive versus indolent disease?

DR. COHEN: That has really been based on the much older studies that were done in the '70s and '80s, following patients that were treated with TUR. In the early reports, in the '60s, it was thought that CIS is always a very aggressive disease, and then over time it has been shown that some have much later progression of the disease, five, six, seven years rather than one, two or three years. There is no way to predict that population.

DR. GULFO: But the recurrence rate during that period also gives insight into what type of disease.

DR. COHEN: Once you have a recurrence, obviously you are selecting out patients that have bad disease, and these are patients in this series who are on their third episode of the disease. They are patients that are clearly not indolent disease.

DR. SCHER: Given the difficulties assessing failure, do you know the time to cystectomy between the

responders and non-responders?

DR. GULFO: Yes, yes. We have that.

[Slide]

Of the 37 cystectomies in 01 and 02, 4 were in responders, 33 in non-responders. The median time from initial entry into the study to cystectomy was 2 years for the responders and 8.2 months for the non-responders.

DR. LAMBORN: I believe that is just for those who went to cystectomy however.

DR. GULFO: Correct, but that is all we have, the 37 who went to cystectomy.

DR. SWAIN: How did you define treatment failure?

DR. GULFO: Treatment failure was defined very conservatively. There are a number of series in this disease that would not have defined Ta disease as failure. I don't believe it is failure, but we used it in the complete response rate. So, Ta is embedded in that. Two positive cytologies is embedded in failure. The danger of that is Harry Herr has shown us that 20%-30% of patients, not even at this stage of disease but one step prior, recur in the upper tract. So, in areas we aren't even treating in diseases that don't kill, we would consider failure for this study.

DR. SWAIN: And nothing else? Nothing else at all, like enterotoxicities or anything like that?

DR. GULFO: Oh, yes, we didn't intend to treat so the four patients lost to follow-up we declared as failures.

DR. JUSTICE: I have a question about slide 90 again. You basically used the Amling data to show that the risk of invasive disease is about the same. But what you haven't addressed yet is what is the risk of metastatic disease in the Amling data. What is the risk of metastatic disease with delayed cystectomy?

DR. GULFO: I need to defer to Dr. Grossman on that. The Amling series -- I have read it several times -- I do not think projected out the metastatic rates.

DR. GROSSMAN: Yes, the pathologic T3 group was looked at because those are the ones that are going to be at greatest risk for late failure, for metastatic disease. And, this is clearly the high risk population. Patients who have more superficial invasion at time of cystectomy still have some risk of having metastases ultimately but the risk is considerably lower.

DR. JUSTICE: But what about the patients who didn't have cystectomy who present with metastatic disease?

DR. GULFO: Oh, the four. Could we show the four? Slide 144, I believe.

[Slide]

Yes, there were 4 patients who ultimately

developed metastatic disease and, as Dr. Temple stated earlier, at a pretty long time since we said the patient failed, clinical failure. So, you know, what is done with the patient is a decision by the patient and the physician that we really have no control over. I will tell you this, that we have analyzed nine ways to Sunday the bad actors, and tried to find out if you can predict for their behavior in every way, and you really can't. The data that we have shown suggests that late failure and delayed cystectomy is better than early failure and immediate cystectomy, which is kind of intuitive and silly. So, what we say is not withstanding these data. We advocate prompt cystectomy in patients with Tis, grade 3 tumors -- anyone with this or greater, and even Ta grade 3. So, grade 3 tumors should go to cystectomy as well. So, we don't advocate failure of the drug in doing this.

DR. TEMPLE: I realize it is not quite perfectly on point, but did Amling have long-term follow-up?

DR. GULFO: If he did, I would have used the same paper for the 5-year survival --

DR. TEMPLE: Right.

DR. GULFO: So, I couldn't use that paper for that. I had to go to Pagano.

DR. TEMPLE: Do you suppose he actually has it somewhere but hasn't published it?

DR. GULFO: You know about these people better than I do!

[Laughter]

DR. GROSSMAN: Well, this is a Duke series and I am sure the data is there. It is just a matter of getting another resident to dig it out and report it. That is ultimately what it comes down to. I am sure the data exists. The problem is it is usually not easily accessible and it takes some work to dig it out.

DR. MARGOLIN: Do you happen to have the data -- many companies do keep this, I don't know if you do -- on how many patients were screened for these two studies in order to get the 90 who went in?

DR. GULFO: Yes, we don't have those data, but it was a very difficult study to accrue because we required very, very poor acting patients. I will ask Dr. Wehle to say a few words about this, but I would get called all the time, you know, "Joe, I have a patient that I gave BCG to in the past twice and I want to put him on the study as Tis." They would send the path reports in and it was only papillary disease. I say, "you can't put that patient on." They say, "come on, this guy's got BCG-refractory Tis." I say, "not by protocol, had to be treated twice in the past." So, if you asked me to guess -- I am just winging this but I would say three:five:one.

DR. MARGOLIN: And, you would like us to believe that the ratio points to a group of patients who was much worse --

DR. GULFO: Absolutely.

DR. MARGOLIN: -- than the community at large, as opposed to being selected for in the way we often see in Phase II trials.

DR. GULFO: In my opinion, without a doubt, but let's ask an investigator.

DR. WEHLE: I think it was a group working at a tertiary center that had a tendency to see the worst patients, or patients who failed and they don't know what to do next. When I saw the protocol, I thought, well, it is going to be very difficult to find enough patients, at least judging from what I see in our practice, to have a number, at least in our institution, to treat. It was difficult because a lot of the patients I think, before they got to us, probably did get a cystectomy. But this group, for whatever reasons, didn't want a cystectomy, or in some of these patients health problems wouldn't allow a cystectomy.

DR. MARGOLIN: So you could certainly say that even though I think your data are very convincing, what we didn't see in terms of those who went to cystectomy in lieu of going to this trial may have also selected in the other

direction.

DR. GULFO: I understand what you are saying, and Dr. Williams can help me with this, our centers were also conducting a study for another drug that this panel reviewed two years ago, and the entry criteria for that were not as stringent as ours. So, our patients, by virtue of a number of carcinoma in situ diagnoses, I think and our experts and investigators and everybody I have talked to thinks are especially poor prognostic patients.

DR. DUTCHER: Thank you very much. I think it is time to take a break. We will be back at 11:00 or a few minutes after 11:00. Thank you.

[Brief recess]

DR. DUTCHER: The FDA review is going to be presented by Dr. Odujinrin.

FDA Review

DR. ODUJINRIN: Thank you very much, Dr. Dutcher.

[Slide]

I will be reviewing the information you have already heard for the FDA.

[Slide]

This slide shows the review team of this drug, and all the members of the team are sitting on that side of the hall.

[Slide]

You have heard a lot of information about the drug already and, as such, I will not bore you with more details of the basic information about the drug. But the proposed indication I would like to point out is that it is for intravesical use in patients with CIS of the bladder who are refractory to BCG immunotherapy, and that is the key point.

[Slide]

Again, a lot has been said about what is known concerning transitional cell carcinoma of the bladder and CIS, and I will just highlight a few points. It is a pan-urothelial disease, and Tis is the most aggressive form of cell carcinoma of the bladder, with 54% to 83% of the patients developing invasive disease in 4 years after surgical therapy only.

[Slide]

TUR, with or without intravesical therapy, is the treatment of choice. Cystectomy, as you have heard, is performed when most of the invasive disease develops. BCG intravesical immunotherapy post TUR has effectively delayed cystectomy in many patients. That is not a controversial issue any more. You have seen data to support that. BCG efficacy over TUR only, however, has been documented through several randomized clinical trials.

[Slide]

Intravesical therapy has not been as successful as BCG either as prophylaxis or therapy of persistent disease. The two most frequently used drugs in CIS are mitomycin C and doxorubicin, or epirubicin in Europe. The efficacy in CIS is really not that clear in the literature.

[Slide]

Therefore, prevention or delay in the disease progression to muscle invasive disease is the most important objective of therapy in this disease, as cure is an elusive goal.

[Slide]

There are many factors that affect the natural history of CIS and suggest a variation in the risk of progression to muscle invasion. Some of them you have heard this morning, and I will just reiterate them. One is multifocality; location, especially in the dome; p53 status, as well as other molecular markers that are evolving as being significant in determining risk factors; and time interval between recurrences.

What all this implies is that we are dealing with a disease of a variable proliferative rate because these are all proliferative indices, and would determine how indolent or aggressive a particular patient's CIS disease would be.

[Slide]

Other causes of variation in reported response

rates in the literature, among them are differences in staging among pathologists. Maybe if Dr. Cohen reviews all of them we would get similar results, but with many different pathologists, we get different interpretations of the same thing.

The same thing goes for surgery. The completeness of TUR affects the response rates reports. Definition of progression also differs. Amount and type of adjuvant therapy given differs. The length of follow-up differs. Unrecognized disease in extravesical urinary tract regions also differs. So, all these factors impact on the responses or the results that are reported in the literature.

[Slide]

There are other therapies that are already available and that are coming. As a regulatory agency, we will be dealing with many of them. Some are interferon, photodynamic therapy, and others are immunotherapy or chemoprophylaxis, such as bropiramine, lactobacillus, and high dose vitamins.

[Slide]

Evaluation of any new treatment modality in CIS has to take into consideration the variable natural history of the disease, as well as diagnostic and follow-up factors that impact on response rates reported in this disease because, as Dr. Grossman pointed out, there are really no

concrete guidelines in this disease. So, we need guidelines to assist us in determining evaluation.

[Slide]

This is a slide that represents the protocol that we are discussing today, protocols A9301 and 9302. Dr. Gulfo has very appropriately gone over this in detail. I will just highlight again some key segments of the protocol.

The study population is in CIS patients who had recurred or failed after multiple courses of intravesical treatment, including BCG and, therefore, were considered BCG-refractory. This was an open-label, single-arm, multicenter study.

[Slide]

The study population is as listed, and as you have heard before. I would like to point your attention to the range of disease duration in years, that ranged from 1 to 27 years. That is, a patient had superficial bladder cancer for 27 years before entry into this study.

[Slide]

Among the inclusion criteria given by the company, bladder mapping with transurethral biopsies of suspicious as well as normal-appearing areas were to be done within 28 days of treatment. Mapping should include the dome, posterior wall, right and left lateral wall, and trigone,

prostatic urethra if clinically indicated. Positive urine cytology at baseline, and to be done less than 28 days prior to the first AD32 treatment.

[Slide]

The drug therapy itself consisted of an 800 mg dose of AD32 diluted to 75 cc and was instilled into the bladder, with a dwell time of approximately 2 hours. A treatment course, as you have heard before, was 6 consecutive weekly instillations.

[Slide]

Efficacy considerations provided by the company are defined complete response as no evidence of disease at primary disease evaluation and at next cystoscopy, 6 months after treatment. NED is defined as complete resolution of all CIS; no recurrence of papillary disease; no new CIS or papillary lesions; all biopsies and cytology specimens are negative for tumor; and 2 consecutive negative urine cytology on patients with positive urine cytology only.

[Slide]

No response or recurrent disease was defined as positive biopsy or positive urine cytology on 2 consecutive visits.

[Slide]

Our review of this submission consisted of a review of the applicant's protocol, some of which I just

mentioned, a regulatory history and a literature review, and you have heard a lot about the literature review this morning.

[Slide]

We have to consider regulatory history, again, because we need guidelines in this disease. In 1988, this was raised before ODAC at that time, and subsequent discussion with Dr. Prout indicated the following: Delay in cystectomy determined by a good CR rate with CRs lasting at least 1 year was suggested as a worthwhile benefit and could be an adequate basis for approval. Persistence of CIS after TUR should be confirmed by positive urine cytology.

[Slide]

Again in 1996, another submission was presented to ODAC, and many of the current members were on that Committee at that time. These were some of the conclusions at that meeting: Patients with diffuse multifocal bladder CIS who have failed or are intolerant of BCG are generally high risk and, therefore, are candidates for immediate cystectomy.

A medical treatment capable of producing durable CR in a substantial proportion of patients could provide meaningful clinical benefit.

However, delay in cystectomy occurring as a result of such therapy should not place patients at unreasonable risk of developing metastatic bladder cancer while

undergoing this medical treatment.

Non-randomized clinical trials could be adequate to support approval of such a treatment.

[Slide]

Some of the key points from the literature have already been discussed, and I will just briefly go over key sections. TUR with fulguration is rarely definitive therapy in diffuse CIS. A schedule of baseline and follow-up cystoscopy with biopsies should be established and should include bladder mapping with adequate number, at least 6, of samples taken from different segments of the bladder. Samples should include some muscle layer to ensure that we are not dealing with muscle invasive disease already. At follow up, areas of previous pathology should be sampled. These criteria are really similar to the protocol criteria of the applicant.

[Slide]

With regard to pathology issues, unifocal versus multifocal disease -- the risk of muscle invasion is different from diffused disease. The differentiation between drug effect and TUR may be difficult in a unifocal setting.

[Slide]

In terms of pathology issues, there is a need for consistency in specimen review. Variability among

pathologists in grading or staging the same specimen often affects results. And, there is a need for central review or blinded review of the specimens.

[Slide]

The method of collection -- voided, catheterized or bladder wash, will determine whether the cytology is meaningful in terms of results. The method of doing the tests, cytospin, flow cytometry of biomarkers, would also affect the results. The timing of collection -- the need for documentation of positive cytology collected at least 24 hours post TUR in patients with unifocal disease.

[Slide]

I will now give the pooled results of studies A9301 and A9302, as the FDA finds them. These are the pooled results of both studies. We utilized all the 20 patients reported as CR by the applicant in determining efficacy, and considered all 90 patients for the safety review.

[Slide]

We considered 7 patients to be true complete responders, and 13 others we were not so certain -- 13 others failed because they were not definite responses, with 6 definitely not responders, 3 not verifiable as per protocol, and 4 with questions. I will go over these patients to indicate why we categorized them as such.

[Slide]

CR was not verifiable as per protocol in 3 patients because of urine cytology of unifocal disease where urine cytology was positive only at baseline and was consistently negative, and 1 patient had a long history of superficial disease lasting 24 years, essentially indicating that this person had an indolent CIS.

[Slide]

There were 4 patients that we had questions about concerning the results. One patient had consistently negative urine cytology, unifocal disease, a long history of superficial bladder cancer for 7 years. Another patient had a long history, 8 years, prior to entry on this study.

[Slide]

A third patient, the last BCG treatment was 2 months before the study, and unifocal disease at baseline, and a long history of superficial bladder cancer, and a consistently negative post-study urine cytology. In a fourth patient the positive diagnosis of CIS at baseline was uncertain.

[Slide]

In terms of safety issues, the drug was well tolerated at the dose given, and there was no evidence of systemic drug effect, except in 1 patient who had bladder perforation and, as such, had systemization of the drug but

the patient recovered uneventfully. He developed myelosuppression which recovered with management. And, there was 1 other patient who had reflux nephropathy as a result of the drug, and that was also an uneventful event.

[Slide]

In terms of progressive disease, 37 patients were cystectomized for disease progression, and 3/37 patients had invasive bladder cancer at cystectomy, with lymphoid involvement in 1 patient.

Four patients died due to bladder cancer. These patients were not cystectomized. The current status of 50 patients, we know now, as of Friday, that 40 of them received other therapy, and 20 of those patients received BCG therapy, as you saw earlier in the presentation.

[Slide]

Determination of remission duration was difficult because of variability in determining the endpoints of treatment. There was also variability in adherence to protocol criteria.

[Slide]

I would like to go over a couple of previous slides that I have shown, one dealing with the toxicity. As I said, it was mild and consisted of cystitis, bladder pain and dysuria, which were tolerable. I already spoke about the systemic absorption in one patient.

[Slide]

There was a total of 10 deaths, and 4 of the deaths were related to bladder cancer, and the status of the other patients we do know about. We know that 20 of them have received BCG post-AD32 study.

[Slide]

So in conclusion, was the study population at high risk of progression? Fifty-three percent of all patients had multifocal disease at baseline and many had a history of multifocal disease. Forty-five percent of those not in CR underwent cystectomy.

[Slide]

So, what was the CR rate? Only 3 patients had CR that we would consider very definite if you require that the baseline cytology was collected after biopsies were performed and was positive. And, 7 patients, 8%, we would, therefore, consider definitely CR. The potential CR was 14% based on the information that I gave you concerning the other 7 patients, if you allow for unifocal disease without documentation of positive cytology after biopsy and allow only a single follow-up biopsy.

[Slide]

AD32 was well tolerated and 8% of the patients were documented to have serious outcomes; 4 died from bladder cancer and 3 had deeply invasive disease at

cystectomy.

[Slide]

Follow-up is inadequate for patients who went off study but did not have cystectomy. Without a controlled trial, it is difficult to assess whether there was or will be an increase in deaths from bladder cancer associated with the delay in cystectomy while receiving AD32. Thank you.

DR. DUTCHER: Dr. Williams?

DR. WILLIAMS: I would like to clarify what was going on up there. We were dealing with two different versions of the presentation. So, you saw a little of the history of our presentation.

But I would like the Committee to look back at page 10 of the handout because the slides that we agree upon are found there.

[Slide]

Beginning with the individual patients that were less than definite, if you look at the bottom, under "group B" there were 3 cases with what we called questionable baseline status, and that had to do with the debate you heard if you have a single focus of recurrent disease and you didn't collect a urine cytology 24 hours after the biopsy, do you really know that you didn't remove the disease? Do you know that you still have it there at 6 months of follow-up? So, that is what that debate was

about, those 3 patients and whether you would classify them as adequately diagnosed at baseline. As you heard, I think it is controversial. It is a difficult issue to deal with. But that is the question on those 3 patients.

[Slide]

The next 4 cases, on the next page, page 11, were the 4 cases with what we called questionable follow-up and, in general, those were cases that had perhaps only 1 follow-up biopsy of the initial site rather than 2, as required per protocol.

[Slide]

Then, the summary of our findings, on page 12, at the bottom of that page, the definite CR was 7/90 patients and, depending on how you calculate the median duration, whether you require a biopsy of the initial site, whether you require cystoscopy with a biopsy of any site, or whether you just follow them until you have recurrence, the duration of either 12, 18 or 21 months in the 7 patients.

If you look at the 14 patients, which is a 16% rate, including the ones where there is some controversy, in those 16%, depending on the method of calculation, the median duration is 13.5, 18 or 21 months duration. So, I just wanted to clarify that. It was just a matter of different versions of power points.

Questions from the Committee

DR. DUTCHER: Questions for the FDA?

DR. MARGOLIN: Mine is very trivial. Did 55 patients have cystectomy, or did 37 patients have cystectomy?

DR. ODUJINRIN: Thirty-seven patients in the two studies had cystectomy. I will let him explain that.

DR. GULFO: In the 02/02 studies, 37 patients went to cystectomy. We included as much cystectomy data as we could get. So, we included the 03 safety study where 20 patients went. So, we tried to give you all the data we could. The rate of pathologic events disease was higher in the 03 study than in the 01/02. So, we felt you would be interested in seeing that.

DR. SCHER: This will get back to the point that I was trying to raise earlier. Isn't the issue not really whether or not a patient had a complete response but what the time was to a clinically significant failure, given that these patients entered the protocol with prior history of multifocal disease in a defined proportion? And, isn't that what you should be focusing on as opposed to trying to worry about whether somebody had a post-TUR bladder wash versus a 24-hour cytology?

DR. ODUJINRIN: Well, we need to have mechanisms of determining whether a patient truly had a response.

DR. SCHER: I am not sure that you do because you

are dealing with a patient population that has a poor prognosis. There is a proportion that will metastasize at some time point without an invasive component. They have already had BCG so, in essence, their clock has been ticking almost from the start of their in situ diagnosis. Again, what you are really concerned about is -- you know, in theory you can make the case for doing cystectomy on everybody at the first CIS diagnosis or perhaps the first failure, and there are prognostic models to address this. But, again, to focus on response rates just seems to me to be the wrong endpoint. And, if you have a proportion of patients within this population where you can clearly show benefit in the sense that they did not develop invasive disease; they did not metastasize at an overly high rate relative to the natural history, then it is just a matter of defining what that proportion is and saying yes or no.

DR. ODUJINRIN: Your point is well taken, but we also need to know how many patients out of the total treated showed benefit.

DR. SCHER: But the CR endpoint in this population should not be a measure of benefit. I mean, standard urologic practice on diagnosis of in situ disease is to intervene. So, again the focus on CR when there are a lot of interpretative issues just seems to me to be incorrect. Now, your point is well taken. You would be more convinced

if patients had systematic biopsies of all sites, whether or not there was something present, at fixed intervals, and that would be, I think, a greater demonstration that, in fact, you had altered the natural history for individual patients because that is really what you are trying to see.

DR. DUTCHER: But I think considering the variability of this group of patients, even in this bad prognosis group, you have to have something you can measure to be able to judge if it is a benefit or if it is the patients.

DR. SCHER: Right. That is the whole point. What you are really interested in is the antecedent history of the patient before they went on study. If somebody had four episodes of in situ disease in a one-year period and intervention X occurred, and finally intervention X didn't happen for two years and there was no evidence that they metastasized or developed systemic disease, I would argue that that was beneficial in that patient.

DR. WILLIAMS: You would call that a response. I mean, what you are talking about is a benefit but how do you prospectively define that?

DR. TEMPLE: They hadn't progressed before or gone on to systemic disease. So, how do you know how long it would have taken them in the absence of therapy? I think

you are defining a sort of vague time to progression endpoint. The trouble is that there is no control group.

DR. LAMBORN: I don't know, I think maybe we are getting over into the Committee discussion but my problem is that while that might be the more interesting, we don't appear, from either the sponsor or the FDA, to have the information necessary. At one point you were talking about how frequently had they had recurrences in the prior year and how did the time to the next recurrence compare. We don't know. We asked and we don't have that. The other thing is the protocol that they chose to go with. So, perhaps we are saying that in the future there is another way to approach this that would be more meaningful, but I am concerned that we can't evaluate that at this point.

DR. SCHER: I don't want to hog the microphone but if you were looking for the treatment effect proposed in this trial and you were going to design a randomized trial for this population, how big would it have to be?

DR. LAMBORN: It depends on how bit a treatment effect --

DR. SCHER: No, based on the null hypothesis within this trial --

DR. LAMBORN: Well, I can't because this trial is based on a response rate --

DR. SCHER: Even based on a response rate, it

would be enormous.

DR. LAMBORN: Shall we come back to that?

DR. DUTCHER: Okay. Other questions for the FDA?

DR. MARGOLIN: I think just that the bottom line is that we don't know at this point of any surrogate for delaying the time until a cystectomy is required because we don't even know when a cystectomy is required. Furthermore, the variability in the natural history of this disease is tremendous and you would have to pre-stratify. If you did a randomized trial, it sounds like you would even have to pre-stratify for duration of disease in some way to select patients with indolent disease from those who need a cystectomy in the very near future.

DR. SWAIN: I just have a minor question. Did any of the 15, 20, 19 or 16 however many complete responders --

[Laughter]

-- we end up with, after they had recurrence receive BCG?

DR. ODUJINRIN: Yes.

DR. SWAIN: How many?

DR. ODUJINRIN: Twenty, I think, is the figure he showed.

DR. SWAIN: No, that is all patients I think.

DR. GULFO: I think it is 4.

DR. SWAIN: And also other treatments?

DR. GULFO: Let me see if we have that. I think it is 4. We can't find the slide. I believe I remember 4 but I definitely remember that there was no difference in the proportion of responders and non-responders getting BCG in follow-up.

DR. SWAIN: Did they receive other intravesical therapy besides BCG?

DR. GULFO: That I don't --

DR. SWAIN: You don't know?

DR. GULFO: No.

DR. MARGOLIN: I have a question, and I guess this would really be more appropriate to the company than to Wole, unless Wole knows. The choice of the dose that was used in this trial, I think somewhere in the package said something about having been selected as the maximum tolerated Phase II recommended dose from the Phase I/II study, and since this drug seems to be so well tolerated and safe, I wonder if there was any information about dose response or anything that would make you think that higher doses might have been associated with an even better response rate.

DR. GULFO: We were limited by the amount of dose that we could give at any one time. I think the Phase I study clearly showed 800 mg in the formulation that we are

using was the maximum we could go. So, no, we went the other way. We tried to say, "gee, if 600 looks good, how about more?" And, we did it in 9303. We dosed for 9 weeks, and we saw that when you gave 700 or more you had more premature treatment terminations.

DR. ODUJINRIN: Also, the alcohol content seems to play a significant degree.

DR. GULFO: Yes, the Phase I study tested three different formulations, and we realized that beyond a certain alcohol limit you had much more toxicity. We reformulated and the 800 mg dose has 13% alcohol and not the 15, and that is why you can only get 800. But at that dose, if I may, that is a tremendous multiple of the cells in culture.

DR. TEMPLE: Do I understand that the follow-up status on patients is that there are 50 of the original 90 that are not fully accounted for, whose vital status is not known? Is that the current state of it?

DR. GULFO: That is not true. The recurrent status is known in 79 patients.

DR. TEMPLE: And that is up to some recent time?

DR. GULFO: Yes, up till April of this year. Sorry, January of this year; our update came in, in April.

DR. TEMPLE: Okay.

DR. DUTCHER: Thank you very much. I guess we

should ensue in some Committee discussion. There were some issues that people wanted to raise before we go on to the questions. Anybody have any issues they want to bring up for clarification? It seems to me that the issue existing is are the patients a defined population that include patients who would go to immediate cystectomy, and if they are, then why is there a plateau on the curve of people that actually did have cystectomy? What is basically the standard of care for confirmation of response, and whether the cytology is an issue? And, what is the risk/benefit ratio for this agent? Anybody want to talk any of these? Go ahead, Dr. Sledge.

Committee Discussion and Vote

DR. SLEDGE: I think there are sort of three general issues that I would like to address. The first is the issue of toxicity. I think you can look at toxicity in two ways here. One is the direct toxicity of the drug. I think that is clearly an acceptable toxicity in this drug. I don't think there is any question about that. The related toxicity, which is the one we have heard, is was there, if you will, delayed toxicity from not having a cystectomy for patients entered into this trial. I personally heard reasonable evidence to suggest that there wasn't any such delayed toxicity, that basically what we were seeing was pathologic upstage. I think that is a reasonable argument.

So, I feel comfortable with this from a toxicity standpoint.

The second issue is the issue of risk. Again, I don't mean risk in the way we usually think of it for chemotherapy drugs in terms of side effects but, rather, risk in this setting of whether or not we can define a group of patients who are at sufficiently high risk that they require immediate cystectomy after having failed BCG. Or, to put it another way, can you separate out the indolent versus the aggressive carcinoma in situ patients? Here, I must say that I am a little bit less convinced, and I am less convinced primarily because of the data that I have heard in patients in follow-up in this trial. That is to say that we have, if I am reading the survival curves here roughly correctly, a 55% plateau at 2-plus years, and it really does appear to be a plateau, as far as I can tell, in terms of patients who have not gone on to a cystectomy at that point. This, despite the fact that only 10% of the patients are still at complete response at 2 years. That strikes me as a fairly striking difference if what we are saying is that CR is something that is important here, and if we are saying that this, indeed, is a group that is at very high risk for requiring a cystectomy.

Beyond that, we have also got data presented here that I think 39 or 40 patients received further intravesical

therapy after having progressed or failed on this study. That would certainly suggest to me that the standard of care in the community for the patients who went on to this trial was that it was reasonable to try something else rather than going straight to a cystectomy.

Now, the third issue I would like to address is the issue of benefit, and that is to say how do you define clinical benefit in this trial? Well, I think, without beating this poor dead horse any more, I don't think that complete response is clinical benefit in this trial, and I think the discussants for the company certainly told us that they never use CR in clinical practice. I don't see any particular reason why we should use it here in this discussion.

What we get down to is the question in terms of clinical benefit in terms of whether or not benefit reflects an improved time to cystectomy. Are we delaying cystectomy for this group of patients? And, basically, the data that we have, as far as I can see, is that non-responders had a median time to cystectomy of 8.3 months. Responders had a median time to cystectomy of 23 months. That basically is the only real data that we have here.

What does that mean? I think thee are two obvious and possible interpretations here. One is that we are seeing a treatment effect there. The other is that we are

seeing a natural history difference between responders and non-responders. And, it is a truism in virtually every clinical trial that responders do better than non-responders, and they tend to do better than non-responders partly because of treatment but also, more commonly, because the natural history of the different groups differs. In a non-randomized trial I am substantially concerned about the possibility that what we are dealing with here are differences in terms of selection bias for responders versus non-responders, and I am just simply not quite sure how we would ever define benefit.

I think if we were talking about a drug where, you know, 50% of the patients were in CR at 4 years, that would be pretty much a no-brainer. I am not at all sure what 10% at 2 years means.

DR. LAMBORN: Could I just do a quick point of clarification? I think that median time to cystectomy that you are quoting is just for those who have had a cystectomy and, in fact, if we look at the median time to cystectomy for the non-responders overall, it is probably substantially longer.

DR. SLEDGE: Correct.

DR. LAMBORN: So, even that apparent difference --

DR. SLEDGE: Is less impressive.

DR. LAMBORN: -- is less impressive --

DR. SLEDGE: Is less impressive than it sounds.

DR. DUTCHER: Dr. Scher, do you want to make any comments?

DR. SCHER: No. I will commend Dr. Sledge on his analysis. I was struggling with essentially the same issues because you are dealing with a disease that is relatively rare, where the practice patterns are not standardized, in a trial that was conducted over multiple centers by multiple investigators, each of whom has his own biases on how to treat a patient, and we are similarly dealing with a patient population that is heterogeneous both in terms of their prior and natural history and their ability to undergo the definitive procedure, namely, cystectomy.

So, what we are essentially being asked is whether it is appropriate to approve a drug on a Phase II indication when we are uncertain as to the natural history of the disease prior to the entry into that protocol.

I have no difficulty with the definition of BCG-refractory as defined in this cohort but, again, it was evident from what was actually done to patients that, in fact, immediate cystectomy was not recommended for a significant proportion.

I feel very strongly that the CR, as we have been wrestling with, is absolutely the wrong endpoint and that we need to focus on something that is clinically important,

either the time to invasive disease, time to metastasis, or bladder cancer mortality which, unfortunately, occurs frequently when patients do metastasize.

I am not certain that if the data weren't analyzed in a different way, which is in part the way it was presented in tabular format, would it be appropriate if you have seen patients who have shown a clear-cut history of recurrence with in situ disease in multiple sites where the protocol required multiple biopsies at multiple sites, were in fact performed on a regular basis on all patients and showed that there was, in fact, a change in the development of new in situ disease which we know is associated with a bad outcome, whether that would not be sufficient to show that this was beneficial.

I think to design a Phase III trial in this population is going to be virtually impossible given the relative rarity and the heterogeneity of the population going in. So, if there is ever going to be an indication for BCG-refractory disease, it will have to be on some Phase II endpoint, and it is probably appropriate to perhaps set that now, and the question would be whether this data could be looked at in an appropriate format.

What did impress me is that the duration of benefit of 21 months, however you slice it in terms of the 13, 18 or 21 months, is real for that proportion of

patients. And, I do recognize the difficulties with responders, non-responders but, again, you are looking for approval of a drug for a proportion. The drug is safe and I am not concerned with that. You look at the experience with IL-2, the proportion of patients of CR is relatively small but, nevertheless, real benefit. So, there is that precedent. And, the question is, is what was demonstrated here today enough, or what should that percentage be? And for this, I would obviously have to turn to the Agency.

DR. DUTCHER: Well, what Phase II endpoint would you like to see?

DR. SCHER: Well, a hard endpoint is time to invasive disease. I don't think anybody would argue that. Or, time to metastasis; delayed cystectomy.

DR. TEMPLE: I am sorry, I am probably being dense but could you say exactly what the study design that you are talking about is? I mean, who is the population that is randomized? Who gets what?

DR. SCHER: I think it would be very difficult to randomized this population. I don't think there are enough patients to do it based on what you would expect the treatment effect to be. If you look at Harry Herr's original series of BCG-treated patients, 86 patients; entry criteria required 4 occurrence within a year prior to enrollment. Those patients with in situ disease had

essentially 40% of their bladder involved with in situ disease, and he was able to show --

DR. TEMPLE: I am not trying to promote a design; I am trying to find out what the design you are proposing is. So, it is not randomized. It is, therefore, historical.

DR. SCHER: I think it has to be historical on individual patients who show a defined pattern of recurrence.

DR. TEMPLE: And, could you say exactly what the comparison is? You take people -- who? Who would you take? People like the ones in this trial?

DR. SCHER: I would probably take -- I didn't see the bladder maps or the antecedent history on the whole population, but it would seem to me that if someone was showing a short pattern of recurrence, say, two or three in situ lesions within a one-year period or a year and a half, those patients were declaring themselves as having a poor prognosis. Then, if you intervened in those patients and a proportion did not recur, did not metastasize, I would argue that that is beneficial. Then the issue is how do you set them up.

DR. TEMPLE: So, you are going to compare their on-therapy course with their previous course?

DR. SCHER: Correct.

DR. WILLIAMS: I guess we are kind of trashing CR.

DR. SCHER: It is a hobby!

[Laughter]

DR. WILLIAMS: I really think that the benefit of having this endpoint we are calling CR is, first, that we think they have the disease at baseline and, secondly, we think that the follow-up was adequate, that we could then put a label on it. So, you know, when you are looking at time to progression you might not have any follow-up. So, this is a way of saying that for a certain length of time there was adequate follow-up that we would call it a CR. Now, if that CR lasts a long time I think we have the same endpoint you are talking about. So, I don't think that it is a bad endpoint.

DR. SCHER: No, it is not a bad endpoint. Point taken. The issue is that this trial, to me, has a component of patients who are being treated prophylactically, yet, who have a defined natural history. And, this gets confused in a lot of the superficial bladder literature. When are you actually looking at response? If you don't have video documentation, and video review of what the lesions are, and biopsies at multiple sites, and clear documentation post-TUR that there is residual disease, then doing a CR endpoint -- or making sure that your patients, in fact, have residual

disease is difficult. So, there is probably a component of patients in this group in whom response cannot be assessed, at least how it was done, but their natural history was, nevertheless, so poor that they did better.

DR. WILLIAMS: So, if we took CR and looked especially at the duration and included only patients that seemed to have a very rapid recurrence rate, that would be the type of trial that would be impressive to you?

DR. SCHER: You could do a CR trial as long as you required clear-cut multiple sites of disease with residual disease, then you could assess response. But with in situ disease the natural history in some patients is very aggressive, so they do invade and metastasize. So, altering that course would be useful.

DR. TEMPLE: Getting back to the design proposed, you would be taking people who had had what seems to be quite a good therapy, BCG, and had begun to fail on it, and then compare the outcome in what is meant to be something of a salvage therapy. This isn't proposed to be a replacement for BCG. There seems a fair chance that it won't do as well as the very first course of BCG.

DR. SCHER: No, it won't.

DR. TEMPLE: So, I am still trying to focus on what you would do if you wanted to do this study. Comparing people with their previous course has actually been used

once or twice in various desperate situations where there didn't seem to be a better design.

DR. DUTCHER: But, don't you think these people -- if you took that same population with four recurrences in a year and a large amount of bladder involvement, they probably wouldn't be put on an investigational drug. They would go to cystectomy. I mean --

DR. SCHER: I know. This is one of the issues that Dr. Sledge raises.

DR. DUTCHER: Yes. Those are the patients where nobody is going to take a risk, and the people that are a little slower going, you can say, well, let's try something else. So, that is where the natural history gets confused with the drug effect, it seems to me.

DR. SCHER: Right, but in a group that is not destined to metastasize in the short term, if you know the antecedent history where that patient is developing multiple in situ recurrences and then they don't --

DR. DUTCHER: So, we need that information.

DR. SCHER: Yes.

DR. DUTCHER: Do you have anything on prior antecedent history in terms of the patients that were on this study that could be used as their own baseline control?

[Slide]

DR. GULFO: This is one of the 7 that were found

to have inadequate -- less than extensive documentation or disease and the patient, in May of '92, had Ta disease; in July of '92, had carcinoma in situ; in June, was treated with BCG, I think; and in June of '93, carcinoma in situ treated with mitomycin; in May of '94, carcinoma in situ again; presents in our study in May of 1994, later in May of 1994 with carcinoma in situ. The patient had positive cytology at baseline; was free of disease in the site of disease, in fact, biopsied at 3, 6 and 12 months; recurred at 18 months with a Ta tumor on the anterior wall and severe dysplasia at another site and a positive cytology. So, here is a patient who every year, twice a year actually for the last year, had carcinoma in situ and had 18 months disease-free on valrubicin.

[Slide]

Here is another patient. This patient received BCG 3 times in the past. So, by definition for protocol entry twice for carcinoma in situ. TCC early on. This is one of the patients I think that was reviewed by Dr. Odujinrin. But then carcinoma in situ in June of '93; then in September of '93. So, got sequential BCGs, as you are supposed; probably got BCG at one of these recurrences here. On study, had carcinoma in situ on the left wall; was biopsied in that area; did not have multifocal disease as defined by having multiple site involvement which, again, is

not multifocal disease; negative cytology at baseline; every cytology was positive; and, you know, this patient is considered to have less extensive documentation of response than the first 7.

I think, as Dr. Grossman stated and other experts to whom we have shown the data, 15 of these patients, regardless of the criteria, were felt to have significant clinical benefit, complete responders in any series of carcinoma in situ. I will ask Dr. Grossman to comment, but the data for the approval of BCG, the SWOG randomized study, required biopsy-proven carcinoma in situ, not documented on multiple sites but biopsy-proven carcinoma in situ. Cytology was irrelevant both at baseline and in follow-up, and the response rates that we all know with BCG were documented in that study.

So, I don't understand. I think that there has been a problem over the years in the guidance document that was shared with us by the Agency in '88, there are so many statements and so many things presented this morning that are straight out of papillary. One of the risk factors for recurrence, presented by Dr. Odujinrin, was p53. Yes, in papillary that is a risk factor; in CIS it is in every patient with CIS. It is the disease. So, I think there are a lot of issues and problems and misconceptions regarding multifocality and risk of recurrence, risk of invasion, risk

of progression. Carcinoma in situ, in and of itself, is a high risk disease. Sixty percent of our patients that failed with Tis or worse or a grade 3 tumor went to cystectomy. Any expert in urology that I have shown this to feels, number one, you know, defining complete response at 6 months was extremely conservative. Nobody else does that, no other series have done that. Number two, the effect that we have seen with the drug is robust and real, and I, frankly, have not seen a study, as we have discussed right now, in the Southwest Oncology Group or other large series where the number of sites of carcinoma in situ, documenting the disease, was a factor. The paper that I highlighted earlier, Gils-Gielen, looked at response and survival and progression, looking at the number of sites with CIS documented by biopsy at baseline and the outcome, and there is no difference. I will invite Mike Wehle and Dr. Grossman to stand up and say -- I think, from what I understand of this disease and hear them talk about, they are grateful when they document it on a biopsy. They know they need to treat this aggressively.

DR. DUTCHER: Can we just get through some of the information?

DR. GULFO: Sure.

DR. DUTCHER: Now, when did this patient get BCG? For the TCC and then for the two episodes of Tis? So, in

'91 and then again in '93?

DR. GULFO: This patient got BCG for carcinoma in situ in December of '93 and BCG for carcinoma in situ in 10/95. No? The patient got successive BCGs, plus maintenance, from 12/93 through 10/95 -- all through out this period. This cannot be right.

[Laughter]

I apologize.

DR. DUTCHER: But essentially two for the in situ and one for the papillary?

DR. GULFO: Essentially, yes.

DR. DUTCHER: So, this is not the same as the four in one year for Tis. So, it is a different -- I mean, it is certainly recurrent Tis but it is a different patient.

DR. WILLIAMS: A two-year interval between the in situ and then the protocol, what happened between '93 and '95. I mean, I am not sure this is the forum to go through individual cases like this, but you do have a two-year interval between the documentation of in situ disease and protocol.

DR. LAMBORN: I think we are all going through the same thing. We are looking at this and saying, based on what is here, it looks more like an example of potentially an instance where individual therapies are carrying them quite a distance, and that is because you don't have the

therapies right in hand. We are trying to plug in when did they get therapy and when were the individual therapies declared failures.

DR. DUTCHER: Right. And, you may well have that data but we can't dredge it right now, but those are the kinds of questions that I think would help us understand where this drug fits. Go ahead.

DR. GROSSMAN: It is true that in the Southwest Oncology trials, which had a lot to do, from what I understand, with getting BCG approved, biopsy-proven disease was the criterion for entry and it didn't matter how many biopsies were positive. So, any biopsy diagnosis of carcinoma in situ was considered carcinoma in situ in those trials.

DR. SCHER: Those were randomized trials though.

DR. GROSSMAN: Those were randomized trials. That is correct.

DR. TEMPLE: I just wanted to follow-up on Dr. Sledge's comments. If I understood you, you are saying that complete response rates are sort of neither here nor there. The point here is to delay cystectomy, and that the evidence that there might be a delay in cystectomy comes from a situation in which people supposedly were just at cystectomy's door but then, when the trial was carried out, it turned out many of them never went to cystectomy even

though they didn't have a complete response. So, the complete response as a surrogate for being able to go along without the cystectomy isn't too persuasive in that setting.

You then pointed out that if you look at median time to cystectomy, that is not very helpful because, among other reasons, a lot of people never went to cystectomy. That sort of invites a time to cystectomy analysis which would include people who never went to cystectomy. And, I don't know whether we have seen that or not, some sort of cystectomy and bladder life-table -- sort of --

[Laughter]

That still doesn't solve his initial problem which is that how soon you get cystectomy may have more to do with the nature of your underlying disease than whether you got the treatment or not, but it does at least put back into the analysis people who never had a cystectomy. Have we seen that sort of analysis? I don't think so. It might have gone by and I missed it. But do you have something like that, sort of a bladder life-table?

DR. GROSSMAN: Let me just mention one thing about cystectomy. The problem, of course, is that we are dealing with people and not a rodent study where you can control variables very well. Here, patients who are candidates for cystectomy and are recommended to have cystectomy frequently

go elsewhere because they don't want to have a cystectomy. So, just because it is an indication and just because it is recommended, it doesn't mean that they are necessarily going to have it. That is one of the reasons people go on these trials in the first place. And, all trials involve, obviously, some election -- why people go on studies as opposed to not going on studies. So, cystectomy is a surrogate outcome and, in fact, of the patients who were candidates for cystectomy, that is the ones who failed with carcinoma in situ disease, 60% did go on to cystectomy, and that is a pretty impressive figure, given the fact that these patients were trying to avoid cystectomy in the first place.

So, I would be very surprised if in a study like this you could ever find 100% of the patients that are ultimately going to go on to cystectomy, even if you told them that they absolutely, 100%, needed it.

DR. GULFO: We did not do an analysis of what you just requested.

DR. TEMPLE: That does seem very important. Medians alone just leave out the half of the patients who never went on to it. So, you don't get any information from them at all. So, that would certainly make some sense if you buy the idea that response isn't the important thing; delay or avoidance of cystectomy is. It still doesn't solve

the problem of the uncontrolled study were responders might well do better for other reasons.

[Slide]

DR. GULFO: But I think that this slide and the time to failure analysis in these patients, to whom cystectomy was recommended for BCG-refractory disease, I think and our experts emphatically feel is very, very impressive, and at no risk -- the risk comparable to the literature, at no risk. And, one of the things that strikes me is if you look at other agents that are being attempted, and Dr. Grossman highlighted them -- mitomycin, which there was no data on, and interferon 12 weeks of therapy, so now the risk is longer than this regimen, initial responses equivalent to ours at 3 months, but then rapid fall-off. Again, I understand it is not a randomized study, but that is the natural history of the disease that urologists are putting on studies in this condition.

DR. DUTCHER: Howard, why could you not do a randomized study in second-line therapy?

DR. SCHER: You could. I just think it would be an enormous trial based on the anticipated treatment effect.

DR. DUTCHER: But what if you are trying to show a certain percentage of benefit; you are trying to basically eliminate the variability of the population more than

looking for, you know, twice the response rate or something like that?

DR. SCHER: Given the heterogeneity of the population and the net treatment effect that you would anticipate with currently available second-line regimens, it would be an enormous study. It would be almost impossible to do.

DR. SLEDGE: The Southwest Oncology Group has done that study in second-line therapy.

DR. SCHER: With no difference.

DR. SLEDGE: That is what I am saying. You would be randomizing to maintenance BCG versus no maintenance BCG which is, in practice, a second-line study.

DR. SCHER: That is third line.

DR. SLEDGE: But I am saying if they already did it, why is it impossible to do it with this drug?

DR. SCHER: Because then you are getting those patients who have now failed the standard of care, which is in some places maintenance BCG. That is the group you are looking at.

DR. SLEDGE: Well, why couldn't you do that trial of AD32 versus maintenance BCG?

DR. GROSSMAN: Well, the maintenance/no-maintenance study was a first-line BCG trial.

DR. SCHER: Right. It is not failures. You know,

this group is further downstream.

DR. SLEDGE: But the justification we heard for this drug is that there is going to be an ever-increasing number of these failures. So, I don't understand why there is a numbers problem here.

DR. SCHER: I mean, there is always a number that show a benefit. But if you accept, let's say, you know, 10% or 15% and you do the duration of benefit --

DR. SLEDGE: What I am saying is we are not talking about a disease where there is -- you know, we are not talking about hairy cell leukemia. We are talking about a disease that we heard is the fifth most common cancer in man in the United States.

DR. SCHER: Not in situ disease. Absolute numbers of in situ disease are relatively small. It is not the total population of bladder cancer patients.

DR. SLEDGE: I would love to hear some idea of what sort of numbers we are talking about. Obviously, if we are talking about a 5000 patient trial, that is not going to be a doable trial. If we are talking about a 250 patient trial, it doesn't strike me as being particularly undoable.

DR. SCHER: Ten percent in two years is what? It is probably around 600, 800 patients.

DR. GROSSMAN: You know, there are 40 institutions

that were enrolling patients in this trial and it took 4 years to get 90 patients. So, yes, it is possible but it is going to take a long time to complete a randomized trial in the setting, and there are patients out there but this is not papillary disease. This is a relatively rare subset, and the numbers, I expect, will be increasing but that still doesn't make the overall N very large.

DR. DUTCHER: I think you already stated this but just remind us. You said 60% who failed with in situ --

DR. GULFO: Or worse.

DR. DUTCHER: -- went to cystectomy.

DR. GULFO: Yes.

DR. DUTCHER: And the other 40% got more BCG?

DR. GULFO: Yes. Well, some of the patients that went to cystectomy ultimately also got some additional forms of therapy.

DR. DUTCHER: Right, but of the 40% who failed --

DR. GULFO: Well, there was one patient I know of because it was a bad actor and I looked at him very carefully, who failed with a Ta grade 3 tumor and got nothing by TURBs for 18 months, and then on a TURB at 18 months had clinical stage 2 disease, and at cystectomy subsequently had pT3a disease with nodes. So.

DR. DUTCHER: But, I mean, of the CIS patients -- those who failed this study with CIS who did not go to

cystectomy, did they all die of bladder cancer?

DR. GULFO: No. No, they are receiving additional therapies in desperation attempts --

DR. DUTCHER: Do they all have active disease?

DR. GULFO: Excuse me?

DR. DUTCHER: Do they all have active disease? I mean, my point is are they again back in this group that are going to be getting an intravesicular treatment every 6 months or 12 months, or were they all just so sick they didn't even go to cystectomy and had very bad disease? I mean, are we seeing again this variability? I mean, I think we are which, you know, is fine but that is just one of the questions.

DR. GULFO: I do not have an answer to that question, other than that they had biopsy-proven carcinoma in situ or grade 3 disease. Those are the ones that we considered were cystectomy eligible, 60 of them, 37 of whom went to cystectomy. The others -- Dr. Wehle, could you talk to us about several of the patients who failed therapy and what you offered them?

DR. DUTCHER: No, I don't think we have time for that right now.

DR. GULFO: So, I don't know. That is why I asked him.

DR. MARGOLIN: One comment and one sort of

suggestion. Although I think we are all very convinced of the safety of this drug in terms of the immediate toxicities and long-term toxicities, I think the claim that -- and although the data would suggest, indeed, that there is not an increased risk of missing the opportunity to cure the patient or to prevent invasive or metastatic bladder cancer, I am not sure that the numbers would actually support that claim. I don't know if Dr. Lamborn has any comments on those numbers, but I think it may be a little risky to claim that this study definitively proves that this second-line treatment does not increase the risk.

The other thing is just in terms of if we are going to design a trial, and since urologists like to do surgery and ultimately we are talking about cystectomies for a large number of these patients, it is conceivable that a with randomized trial with an intervention, followed by an intent to perform cystectomy based on clear-cut criteria that are delineated in such a protocol one could follow the intent-intent-to-treat population, what happens at cystectomy and what happens to the patients who do not go on to cystectomy, even having met the medical or oncologic criteria, and that would perhaps be the way to get such a study done.

I think we are seeing a tiny, tiny percentage of patients who need to be studied, actually taking part in a

study. So, the question we may be trying to answer doesn't really pertain to the community at large.

DR. GULFO: I don't think that one could stratify patients. I would ask, if you would allow, Dr. Grossman to say a work about that I don't think patients can be stratified to say you are definitely going to cystectomy. So, I just don't know how to do that study.

DR. MARGOLIN: No, but you could ask some questions about why they didn't and what happened to them after that, which we don't have here.

DR. DUTCHER: Are there any more pieces of data that we need before we discuss the questions? No? All right, thank you. I think we need to address the questions that the Agency proposed. I appreciate the discussion because I think it is important for us all to have a sense of the disease process and what we are trying to do with treatment at this stage of the disease in this clinical setting.

So the first question, did the 90 patients who received intravesical treatment with AD32 in studies 9301 and 9302 have CIS of the urinary bladder that required consideration of immediate cystectomy because of the risk that they would develop invasive or metastatic bladder cancer? Dr. Scher?

DR. SCHER: I think the answer to that question is

no, just on the basis of what was actually done in the study in that a significant proportion of patients who failed did not go to immediate cystectomy.

I think the question still gets back to the patients who appeared to benefit, were they a group in whom the only other option was cystectomy? And, I am not sure we have all the information to address that right now.

DR. DUTCHER: Anyone else want to comment?

[No response]

All those who would vote no on that question?

[Show of hands]

Ten voting no. I assume Dr. Krook is abstaining because he just got here.

DR. KROOK: Right.

DR. DUTCHER: Dr. Temple?

DR. TEMPLE: I just want to be sure we understand. That is because of the way the outcome was. It turned out that when they failed, not all of them or not even almost all of them went right on to cystectomy? That is the reason for thinking that? I just want to be sure we understand. I am not arguing; I just want to be sure we understand the vote.

DR. DUTCHER: The vote, I think, reflects two things. It reflects the fact that retrospectively looking at it, a large group of patients did not go to cystectomy.

It may also reflect why these patients are in this study.

DR. SCHER: You are raising an important question though because, in fact, they were eligible for cystectomy based on the fact that they had recurrent in situ disease.

DR. DUTCHER: Right.

DR. SCHER: So, the answer to that is a categorical yes.

DR. TEMPLE: So, they were candidates but they still had some choice in the matter and opted for other things. I guess one implication is that that really does leave open the opportunity to compare more than one therapy since apparently at least some of these people were willing to try a whole bunch of things.

DR. SCHER: It is still going to get back to the number of patients available relative to what your effect size is going to be.

DR. DUTCHER: I think that it also reflects the discussion of what is the real risk, and how do you determine who is at risk, which is difficult. Is that accurate?

DR. SCHER: Yes.

DR. DUTCHER: Are studies 9302 and 9302 adequate and well-controlled studies, providing substantial evidence of the safety and efficacy of AD32 in the treatment of BCG-refractory carcinoma in situ of the urinary bladder?

Specifically, do the studies show that in patients with CIS of the urinary bladder who are candidates for immediate cystectomy, the findings described represent sufficient benefit to support approval, considering the potential risk of invasive or metastatic disease when cystectomy is delayed, the observed toxicities of AD32 and the morbidity of cystectomy?

Let's do two parts. Are these adequate and well-controlled trials? Let's start with that. Comments?

DR. SLEDGE: I guess the question is adequate to what purpose. Were the trials reasonably well done? Yes. I don't have any problems with that. Are they adequate to demonstrate a clinical benefit? No, in my mind.

DR. DUTCHER: Because? Not enough numbers?

DR. SLEDGE: Because it is so difficult here to describe what actually represents clinical benefit. If clinical benefit is defined solely in terms of a complete response rate, they have established a complete response rate. If we define clinical benefit in terms of prevention of some significant event, be that event cystectomy or development of muscle wall invasive disease or death of the patient, to say three significant events, I don't think we have adequate data here to demonstrate that. I don't think this trial was adequate to demonstrate that.

DR. DUTCHER: Any other comments?

DR. LAMBORN: I think that is probably an excellent summary because, on the one hand, if you try to look at complete response the percentage of complete responders is marginal, and if we look for other endpoints what I am hearing is that we can't define well enough with this population, at least with the data that we have been given to date, what proportion actually did get a clinical benefit by another measure.

DR. SCHER: What is the bar that will go in a Phase II study because I still don't think you will be able to do a randomized trial in this population?

DR. DUTCHER: They may have the control data but you would prefer it to be individual patient to be able to say that there is a change in behavior of the disease?

DR. SCHER: Again, if you look at the initial hypothesis of the study, you did not anticipate a very high degree of benefit, yet one which could be meaningful, and you could talk it out. Obviously, if you get complete remission that never recurs, and the bladder never has to come out, and there is never metastasis and there is 10 years of follow-up then there is no issue. The question is what is the bar when you have a small proportion of patients who, to my review, clearly did benefit, and at what point do you say that that is adequate for approval, short of a randomized trial which I would argue you can't do in this

population? If it is 10%, then how do you define that 10%? The endpoint of when somebody develops invasive disease is variable. We saw that patients did not get immediate cystectomy. So we know that it is heterogeneous. Again, I would still make the argument, or put it on the table, if somebody had multiple episodes of in situ disease prior to study and then didn't, would that be sufficient?

DR. LAMBORN: I have a question. I have heard you say that if they had multiple frequent repeat episodes and then they had a sustained period without that, and you are also saying there are some patients who met that criteria here but I didn't --

DR. SCHER: I am not sure they did.

DR. LAMBORN: Ah, that is my issue.

DR. SCHER: That is what I would still like to see, what was the antecedent history of the population --

DR. LAMBORN: On a patient by patient basis.

DR. SCHER: Right, exactly.

DR. WILLIAMS: Dr. Scher, how many such patients would you like to see in a population of 90? Or, how many such patients would you like to see out of how many?

DR. SCHER: Well, I will throw it back to you. How many patients who met those criteria, poor prognosis, and then you altered those prognosis would convince you to approve a drug? Is it 5%? Is it 10%?

DR. WILLIAMS: That is what we are asking you.

[Laughter]

DR. SCHER: Again, if you look at IL-2 --

DR. WILLIAMS: We are asking for your clinical judgment. In a population of patients you were treating, what would be the threshold where you would take some risk and delay their cystectomy?

DR. SCHER: I think delay realistically is minor and doesn't impact on the natural history of this disease, and probably on the order of 10% or 15% would certainly make it --

DR. WILLIAMS: So, 10% or 15% with people with particularly aggressive historical findings, and 10% or 15% with an impressive --

DR. SCHER: Particularly with the safety profile.

DR. TEMPLE: This is unusual because we haven't dealt with CIS of the bladder that much, but this is your classic Phase II versus Phase III oncologic trial. You can measure responses in a Phase II trial and generally believe them, and the question always is does that correspond to some clinical benefit, and in many situations it is hard to know the answer to that on such things as time to progression and survival without a concurrent control group and, of course, there is no concurrent control group here.

So, what I hear is two different comments, one of

which is that it isn't obvious that any of these people benefit because it is very hard to tell what they would have done without the intervention --

DR. SCHER: There is still additional data that could be looked at to answer that question.

DR. TEMPLE: Okay, but the alternative is, from you mostly, that says you could deduce that some of these people -- you either can already or you could if you looked at their prior history or something, deduce that some of these people obviously did benefit, the way durable response in testicular cancer might be persuasive even though there is no concurrent control group. Previous versions of this Committee have accepted that as persuasive because that seemed at odds with the natural history and there are sort of self-evident benefits of that. I mean, this is one of those discussions, how persuasive are any of those as an obvious clinical benefit when you don't have a concurrent control group? Can you reach that conclusion? A hard question!

DR. DUTCHER: Well, I think the issue that Dr. Scher raised is that you do have some people with two years on this drug who haven't had any further treatment. So, is it them? Is it the cystoscopy? Is it the drug? Is it the biopsy, the multiple biopsies? I mean, from hearing how this disease is treated, those seem to be very difficult

things to sort out. They are confounding.

DR. TEMPLE: Dr. Sledge, do you find the 11, 14 or 15, or whatever the right number is, those people who had a reasonable history suggesting they were going to have problems and who have now gone some period of time, a variable period of time, without further therapy, just with this, persuasive benefit in the absence of a concurrent control group? I mean, sometimes things are obvious even without a control group; sometimes not.

DR. SLEDGE: If we are talking about testicular cancer where the historical data was that 80% or 90% of 20-year olds with the disease died without therapy and then 80% are cured with therapy, I think that is pretty straightforward. I don't think it is particularly straightforward when you are talking about carcinoma in situ where the natural history is that the time to death here would be many years and, indeed, as we have seen, the time to invasive bladder cancer or something requiring a cystectomy obviously, for this population, was at least 2 years for a substantial percentage of the population.

So, I mean, I have real trouble getting a good handle on what the real clinical benefit is here. With all deference to Dr. Scher, I don't see why this is a particularly difficult group to do a randomized trial in. I mean --

DR. SCHER: It is not a question of it being difficult; it is a question of what is your anticipated benefit for the group to design a study so that it is not an enormous number of patients. Again, 40 centers and 90 patients in 4 years gives you an index of the difficulty of this group.

DR. TEMPLE: Well, suppose you just wanted to see in a randomized trial comparing this with, say, mitomycin, BCG or whatever the alternatives are time to cystectomy.

DR. SLEDGE: I don't see why that would be particularly tough.

DR. TEMPLE: Would that be hard? You expect quite a large difference. So, it might not take very many patients.

DR. SCHER: Well, the BCG effect in third-line was about 10%.

DR. TEMPLE: Well, we are talking about low percentages in responses and a fair fraction of people who fail --

DR. SCHER: Right, if you are looking at 15% versus 10%, that is a factor of 5% difference.

DR. TEMPLE: These are people who failed BCG.

DR. SCHER: Right, but you just proposed a trial with BCG as your control arm.

DR. TEMPLE: Only because a fair number, 20 or so,

went on that when things got difficult enough so, obviously, somebody thought they might respond. I don't know if that is the right design.

DR. SCHER: It is too small.

DR. DUTCHER: Shall we vote on whether these are adequate and well-controlled studies? All those who think that these are adequate and well-controlled studies to assess safety and efficacy, please --

DR. WILLIAMS: I would like to make sure you ask the full question because I think the full question here is important.

DR. DUTCHER: All right. What do you want?

DR. WILLIAMS: I mean, FDA has made it its position that they are adequate and well-controlled given a certain response rate and certain results. I mean, this whole question about the introductory paragraph states that the design was acceptable, given that, you know, this population was heading for cystectomy. So, I just want to make sure you are asking the whole question, which is that it is adequate and well-controlled and the results show --

DR. DUTCHER: But can we stop at one question mark, or do you want both question marks?

DR. LAMBORN: The second question is really your question, isn't it?

DR. WILLIAMS: We made this into one question.

Originally it was two.

DR. TEMPLE: Just a little history, our rules say that any one of a variety of study designs can be a well-controlled study depending on whether the circumstances are appropriate. So, these historically controlled trials, they could be well controlled if the right endpoint were studied; if it is not confounded by the possibility of different responses in responders and non-responders, and all these kinds of things. So, it is really is this an appropriate trial for the question? Then, as Grant says, sometimes the results have something to do with whether it is persuasive. If everybody responded you would say, "Holy Cow!" and say, "yeah, that looks good." If the response rate is lower you might have reservations about it. So, it is a complex question but all that stuff is in it.

DR. DUTCHER: It is based on your previous delineation of how to design a trial for this disease. So, really you are right, it is the second half of that paragraph that we want to ask.

So, do the studies show that in patients with CIS of the urinary bladder who are candidates for immediate cystectomy, the findings described represent sufficient benefit to support approval, considering the potential risk of invasive or metastatic disease when cystectomy is delayed, the observed toxicities of AD32, and the morbidity

of cystectomy?

I think you have to add a clause, the potential ability to take other forms of treatment. But we can leave it like it is. All right, any discussion? No? How many would vote yes?

[No response]

There are no votes for yes. How many would vote no?

[Show of hands]

Ten no. One abstained.

DR. SCHER: Can I ask one more question? Is there any additional information that might change this outcome, given that the Agency had accepted these trials?

DR. WILLIAMS: I am assuming the results have a great deal to do with it in terms of the various response rates, and if there is some other element that is very important in this consideration we would like to hear about it.

DR. DUTCHER: I think what he suggested originally is perhaps a more detailed analysis of each individual patient in terms of how frequently they were recurring.

DR. WILLIAMS: But unless we can get some idea of what kind of results you think would be persuasive, we would have to bring it back to the Committee I guess.

DR. SCHER: I think there are additional analyses

that can be done that might shed some light on whether or not the natural history was perturbed, and that is on the antecedent history of the patient.

DR. WILLIAMS: Ten or fifteen percent --

DR. DUTCHER: Maybe even less.

DR. SCHER: Maybe less.

DR. TEMPLE: So, just to be specific, you think it may be possible to look at the antecedent history and make a persuasive case that at least some of the individuals, now considered responders, might have clearly benefited; that it would be so at odds with their previous history -- possibly.

DR. SCHER: This fixation on responders --

DR. TEMPLE: Well, those strike me as the candidates --

DR. SCHER: I know.

DR. TEMPLE: But if there are others you want to look at --

DR. DUTCHER: Even the others that didn't go to cystectomy. I mean, if there was a change in their time to progression, such that they were just being fulgurated or not even.

DR. WILLIAMS: But they were looked at 3 and 6 months and then they were not CRs on the basis of those early follow-ups.

DR. DUTCHER: And they got other treatment.

DR. SCHER: It seems to me that at some point you are going to have to address the issue of, number one, is the only trial that is appropriate for this population a randomized trial, yes or no? If not, what is the bar in the non-randomized setting? I think the bar that is defined here is not the right one, which is to look at CRs.

DR. TEMPLE: But, you know, if what you are trying to figure out is whether you can delay cystectomy, it is really hard to think how you can do that without a randomized trial. Maybe there is a way. But you can sort of measure responses without a controlled trial, sometimes. You may not be persuaded in this case but at least you can do it. But it is very hard to measure survival unless it is just way, way different.

DR. SCHER: The decision might be that the only way to do these trials is to require a positive biopsy, at least two sites of in situ disease that are confirmed, some visual documentation that can be independently reviewed. That may be it. But I think the bar should be set, either one or the other. That may not happen until the next proposal comes through but, again, the whole issue in the superficial literature separating out true prophylaxis versus therapeutic gets really mixed up in virtually all stages. So.

DR. TEMPLE: But the endpoint you are talking

about trying to evaluate, in whatever design, is time to cystectomy? I mean, you have to have an endpoint.

DR. SCHER: It has to be cystectomy, or it will obviously require closer monitoring of the group that presumably failed the intervention to see what happens.

DR. TEMPLE: You think there may be some way to have a one-group study in which you could conclude the time to progression, time to cystectomy has been delayed? I mean, that is a challenging study design issue I think.

DR. WILLIAMS: I think you are talking about modeling individual patients, recurrence versus previous history of recurrence.

DR. DUTCHER: That is safer because with the other one you are going to have subsequent treatments that are going to confound the specific drug effect.

DR. SCHER: Presumably not that much for this population.

DR. DUTCHER: You don't think so? Dr. Schilsky?

DR. SCHILSKY: I just have a question for Dr. Scher. It has been very interesting to me to hear all this discussion with a lot of experts around the table. I am wondering, given the heterogeneity of the patients and the heterogeneity of the medical practices in this disease, whether you think that an appropriate control arm in a randomized study could be to randomize patients to physician

discretion with respect to therapy? In other words, if the criteria for entry on study were very rigorously established and patients were randomized to, say, valrubicin versus physician discretion so that, you know, some of them might get BCG some more, some of them might get mitomycin, some of them might get immediate cystectomy, whatever, the follow-up specified would be rigorously controlled in the protocol so that the patients would be monitored in the same way at regular intervals in both arms of the study? Then you might have time to cystectomy as an endpoint. Would that be a reasonable way of constructing a randomized trial?

DR. SCHER: I think the trial design is a good one, but if you look at the net benefit that you would anticipate, it is going to be too small to complete in a timely fashion. If there are 10%, 15% or 5% with a safe drug who clearly benefit, where you are dealing with an alternative, a surgical procedure that has a high mortality, would that be acceptable to have this available as an option? And, I would argue that for some patients it would. It is really going to be a matter of where you set the bar to be. So, if it is 10/100 with a safe intervention, where the morbidity of the alternative is significant and not zero, is that enough to get a drug approved? I don't know. I am just posing it as a question because I think doing the randomized trial your design is excellent. But, given this

group, it is very hard to do, particularly if you are looking for 10% effect.

DR. OZOLS: The other issue is the very slow response rate. When we approve very low response rates it is where there is no alternative. I guess that is what Rich was getting at.

DR. SCHER: Right, then obviously the history going in has to be very, very rigidly defined as poor, and I am not sure we know that for all these patients given what happened post-treatment.

DR. DUTCHER: Thank you, all, for your discussion and your comments. It has been a very thought-provoking discussion. We are going to have a lunch break. Be back at two o'clock.

[Whereupon, at 12:50 p.m., the proceedings were recessed, to be resumed at 2:00 p.m.]

AFTERNOON SESSION

DR. DUTCHER: We will start with the afternoon presentation. This is to consider a supplemental application for Taxotere in locally advanced or metastatic breast cancer, change in indication. We will begin with the sponsor's presentation.

Sorry, time out. We will introduce some new people at the table, our new patient representative and some other people from the FDA who are with us now. Could you just introduce yourself and where you are from?

MS. ZOOK-FISCHLER: Sandra Zook-Fischler. I am a patient advocate. I am with Schere Self-Help for Women, in New York, Breast Cancer and Ovarian Cancer.

DR. SCHILSKY: Rich Schilsky, medical oncologist from the University of Chicago.

DR. DUTCHER: Go ahead. We will just do everybody again.

DR. LAMBORN: Kathleen Lamborn, University of California, San Francisco.

DR. OZOLS: Bob Ozols, Fox Chase, in Philadelphia.

DR. DUTCHER: Janice Dutcher, Albert Einstein, New York.

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

DR. MARGOLIN: Kim Margolin, City of Hope, Los Angeles.

DR. KROOK: Jim Krook, a medical oncologist.

DR. BEITZ: Julie Beitz, medical team leader, FDA.

DR. GRIEBEL: Donna Griebel, medical officer, FDA.

DR. JUSTICE: Bob Justice, Acting Director, Oncology, FDA.

DR. TEMPLE: Bob Temple, Office Director, FDA.

DR. DUTCHER: And, we do have to read another conflict of interest statement, so we will start with that.

DR. 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 for the meeting and all financial interests reported by the participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for a conflict of interest at this meeting, with the following exceptions:

Full waivers have been granted to Sandra Zook-Fischler, Dr. Robert Ozols, Dr. Kathleen Lamborn, Dr. Janice Dutcher and Dr. Kim Margolin. A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12-A30 of

the Parklawn Building.

In addition, we would like to note that Dr. Sandra Swain has excused herself from participating in the discussions concerning Taxotere. Further, we would like to disclose for the record that Dr. Richard Schilsky and Dr. Robert Ozols have interests which do not constitute a financial interest in the particular matter within the meaning of 18 USC 208, which could create the appearance of a conflict. The Agency has determined, not withstanding these interests, that the interest in the government and Dr. Schilsky's and Dr. Ozols' participation outweigh the concern that the integrity of the Agency's programs and operations may be questioned. Therefore, Dr. Schilsky and Dr. Ozols may participate fully in today's discussion and vote concerning Taxotere.

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

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

DR. DUTCHER: Thank you. Now we will begin with the sponsor's presentation.

NDA Supplement 20-449/5-055, Taxotere (docetaxel) for Injection Concentrate

Introduction

DR. CHAIKIN: Good afternoon, Dr. Dutcher, Dr. Somers, members of the Committee, Dr. Temple, members of the FDA Taxotere review team, ladies and gentlemen. My name is Dr. Philip Chaikin, and I am Vice President for Clinical Development at Rhone-Poulenc Rorer Pharmaceuticals.

[Slide]

It is my pleasure to introduce this afternoon the presentation regarding our NDA, 20-449, Supplement 5, for Taxotere. Taxotere for injection concentrate was unanimously recommended for approval at the October 17, 1995 ODAC meeting, and FDA granted marketing authorization on May 14, 1996 for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.

This authorization was granted under Sub-Part H of the Federal Code, which allows for accelerated approval of new drugs for serious or life-threatening illnesses. Associated with this accelerated approval, it is RPR's commitment to provide further adequate and well-controlled

studies to verify and describe the clinical benefit of Taxotere.

Today, we are pleased to present the results of two pivotal Phase III trials, namely, TAX 304, which compares Taxotere to the combination of mitomycin and vinblastine in patients with metastatic breast cancer after failure of an anthracylcine-containing regimen, and TAX 303, which compares Taxotere with doxorubicin in patients with metastatic breast cancer after failure of an alkylating agent-containing regimen.

This same commitment was also associated with the conditional approval of Taxotere in the European Union. On March 25 of this year, the European regulatory body voted to lift the conditional approval and grant full approval for Taxotere in the 15-member states of the European Union, and the European labeling has been expanded to reflect the data contained in these two studies.

Taxotere is currently approved in 69 countries worldwide. As of the end of 1997, an estimated 86,000 patients worldwide have been treated with Taxotere and their fight against cancer.

[Slide]

We appear before you today to accomplish two objectives. First, based on the successful completion of study Tax 304, as will be demonstrated today, we ask that

Taxotere now be recommended for full approval.

Secondly, based on the results demonstrated in the patient populations treated in TAX 303 and TAX 304, we are seeking the expansion of the current indication to include patients whose disease has progressed following previous chemotherapy.

[Slide]

TAX 304, Taxotere versus mitomycin C and vinblastine in metastatic breast cancer patients after failure of an anthracylcine-containing regimen is presented here to support the full approval of the current indication. In fact, it confirms the safety and efficacy of Taxotere in metastatic breast cancer patients whose disease is resistant to an anthracylcine-containing regimen, which is the patient population included in the currently approved labeling based on Phase II data.

In addition, TAX 304 provides further evidence for the activity of Taxotere, which supports the expansion of the current label to include patients previously exposed to an anthracylcine-containing regimen.

[Slide]

We will also present data from TAX 303 comparing Taxotere versus doxorubicin in metastatic breast cancer patients which will support further expansion of the indication of Taxotere to those patients in whom an

alkylator agent-containing regimen has failed, whether progression followed adjuvant treatment or treatment for advanced disease.

[Slide]

The indication in the current Taxotere package insert states that Taxotere for injection concentrate is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracylcine-based therapy, or have relapsed on anthracylcine-based adjuvant therapy. We are now seeking an expansion of this labeling, underlined here in yellow, to include patients with locally advanced or metastatic breast cancer after failure of previous chemotherapy.

This afternoon you will hear presentations regarding the efficacy and safety data for both pivotal trials. In addition, we will place these data into context as part of the comprehensive safety database we have amassed as a result of the worldwide use of Taxotere.

[Slide]

So, our agenda is as follows: Dr. Kathleen Pritchard, from Toronto-Sunnybrook Regional Cancer Center, in Ontario, Canada, will provide you with an overview of chemotherapy in advanced breast cancer. Dr. Pritchard was the study chairperson for one of the pivotal trials presented here today. Dr. Matti Aapro, co-chairman of TAX

304, from the University of Geneva, in Switzerland, will discuss study TAX 304, and Dr. John Crown, one of the senior TAX 303 investigators, from St. Vincent's Hospital in Dublin, Ireland, will discuss study TAX 303. Thereafter, Dr. Pritchard will return to the podium to put the data presented here today into context, and I will conclude with a review of the integrated safety data. We will then be happy to take your questions.

[Slide]

We have several experts with us here today to help in fielding your questions, and their names are listed on this slide and the next slide.

I would like to thank all of you for your time and attention. I would also like to thank the FDA Oncology Division's review team for their rapid review of this application and for their expertise and guidance along the way.

So, now I would like to turn the presentation over to Dr. Pritchard.

Overview

DR. PRITCHARD: Thank you very much and good afternoon. It is a pleasure to be here.

[Slide]

What I would like to do in the next few minutes is to put the presentations you are going to hear into

perspective in terms of our current knowledge about the role of chemotherapy in women with metastatic breast cancer.

[Slide]

First, metastatic breast cancer remains a major medical problem. More than 1800 new breast cancer cases will develop every year in the United States and, in spite of advances in early detection and screening, more than 40% of these still will ultimately develop metastases.

Although the behavior of

DR. MARGOLIN: metastatic disease, once it develops, can be very heterogeneous, once a woman with breast cancer does develop metastatic disease, her median survival is only around 2 years.

[Slide]

Chemotherapy for metastatic breast cancer remains largely palliative, although some studies have shown modest improvements in survival. Standard first-line regimens include alkylator agent-containing regimens, such as CMF or CMF-based combinations, and anthracylcine-containing regimens, including single-agent doxorubicin, 5FU, doxorubicin and cyclophosphamide and doxorubicin and cyclophosphamide. It is a reasonably widely accepted view that doxorubicin has been considered the most active agent for the treatment of metastatic breast cancer.

[Slide]

After alkylator agent failure, doxorubicin, either as a single agent in doses of 60 or 75 mg/m^2, or in combinations in regimens such as FAC and AC, has been standard. Doxorubicin usage, however, has been limited by cardiotoxicity, which has been well documented to be related to total cumulative dose but may sometimes be unpredictable and may occur early.

Many Phase III studies have compared different agents, such as mitoxantrone, epidoxorubicin and other agents, to doxorubicin without demonstrating any advantage in efficacy.

[Slide]

As a result, when we looked at designing studies to establish the role of Taxotere in the treatment of women with metastatic breast cancer, it seemed clear that there were two comparisons that needed to be made.

The first was the role of Taxotere in comparison to an anthracylcine or to an anthracylcine-containing combination in the treatment of metastatic breast cancer. As you will hear during the second study presentation, the TAX 303 study was designed to make this comparison. It was decided to compare Taxotere directly with doxorubicin in an effort to determine the relative roles of these two drugs as single agents in this setting.

[Slide]

After anthracylcine failure, there has been really no one standard approach. Available regimens have included mitomycin C and vinblastine, 5FU or methotrexate-5FU with or without leucovorin and the taxanes. But most of these treatment regimens were based on the results of only Phase II studies. There are few Phase III studies done in this group of women after anthracylcine failure. In particular, no Phase III studies comparing taxanes to any other chemotherapy regimen were carried out prior to the study that is going to be shown to you today.

[Slide]

Phase II trials of Taxotere in anthracylcine-resistant metastatic breast cancer, which were the basis of an accelerated FDA approval, showed relatively high response rates, around 41%, with median time to progression, median survival and 1-year survival that looked quite encouraging as well. Based on this data, it was decided to tax Taxotere in the setting of anthracylcine-resistant disease in comparison to a standard second third-line chemotherapy regimen.

[Slide]

Although there was considerable discussion about what that standard regimen should be, we chose the combination of mitomycin C and vinblastine as originally developed at MD Anderson Cancer Center. This combination

has been a commonly used standard regimen, as documented in many reviews, such as Craig Henderson's "Metastatic Therapy" chapter in his textbook, Breast Diseases. The data on mitomycin C and vinblastine in anthracylcine-resistant metastatic breast cancer patients relates to Phase II studies of these drugs used in a variety of schedules. Response rates in these trials range from 7% to 40%. Once again, as I pointed out earlier, this is a poor outlook group of patients but a very heterogeneous group, and it is not surprising, I think, to see that the results in response rates vary quite a bit from one trial to the next.

[Slide]

Thus, it was felt that after failure of an anthracylcine regimen there was no standard treatment available that had been compared to other treatment options, but that a comparison such as the one you are about to see between Taxotere and mitomycin C and vinblastine would provide useful and interpretable data. Hence, the second question and the design of the TAX 304 study which will be presented next.

Now I would like to introduce Dr. Matti Aapro, who will be showing the results of the TAX 304 study.

TAX 304 Study

DR. AAPRO: Thank you, Dr. Pritchard. Members of the ODAC Committee, dear colleagues, ladies and gentlemen,

it is a great pleasure and responsibility to present the results of the efforts of many researchers and patients who participated in this study.

[Slide]

The study, code name TAX 304, compared Taxotere to the combination of mitomycin C and vinblastine in patients with metastatic breast cancer after anthracylcine treatment failure.

[Slide]

As Dr. Kathy Pritchard pointed out, there has been no standard therapy for patients whose disease progresses after anthracylcine treatment. There are a few Phase III studies available in this setting, and none compares taxanes to other agents. We had several discussions at investigators' meetings at the time of study design, in 1993. We finally arrived at the consensus that of the available options mitomycin C and vinblastine was the one treatment that all could agree on as the most widely used, and as an appropriate control arm.

[Slide]

Patients and investigators from 50 centers in Europe, Canada and South Africa participated in this randomized study comparing the intravenous administration of Taxotere, at the 100 mg/m^2 dose over 1 hour every 3 weeks, to the combination of mitomycin C administered every 6 weeks

and vinblastine administered every 3 weeks. For purposes of this protocol, a cycle was defined as the 3-week period between treatments. Please note that prophylactic G or GM CSF were not allowed.

[Slide]

The study was stratified by center. Five days of corticosteroids, starting the evening before infusion, were given in the Taxotere group. Because of the risk of cumulative lung toxicity related to mitomycin C, a maximum of 10 cycles was set for both arms to ensure comparability. Evaluation of response was to be done on a fixed schedule, as shown on the slide.

[Slide]

The primary endpoint was time to progression, and secondary endpoints included response rate, time to treatment failure, survival, safety and quality of life using the EORTC QLQ-C30 instrument. All presented analyses were performed as intent-to-treat.

[Slide]

All patients eligible for the study had to have progressive metastatic breast cancer and have been treated with a prior anthracylcine-containing regimen. Usual organ function criteria had to be fulfilled. The Karnofsky performance standards could be as low as 60. Measurable or evaluable disease was needed, and patients could not have

had prior treatment with the study medications or their respective class of compounds.

[Slide]

Between July, '94 and February, '97 a total of 392 patients accepted to participate in this study. The analysis report had a cut-off date of September 15, 1997. The population is balanced for age and Karnofsky performance status.

[Slide]

For the purposes of this study, resistant disease was prospectively defined as relapse while on adjuvant therapy within 12 months of the end of this treatment, or disease progression on chemotherapy for metastatic breast cancer, or occurring within 30 days of such treatment. Not resistant disease was defined as disease progression more than 30 days after chemotherapy for metastatic breast cancer. Please note that patients who relapsed more than 12 months after adjuvant treatment were not eligible for this study unless they received an anthracylcine for treatment for metastatic disease.

[Slide]

The groups were well balanced for characteristics of prior therapy, and 57% and 56% of the patients were resistant to anthracylines as per the previous definition. The majority of patients had received treatment in the

advanced setting, and about a third of the patients received chemotherapy in both the adjuvant and advanced settings.

[Slide]

Almost three-quarters of the patients had poor prognostic factors, including half of them having liver involvement. While in the MV arm there is a trend for more bone involvement, a factor usually associated with longer survival, this arm also has more patients with 3 or more organs involved. This difference between the 2 arms is statistically significant. This imbalance has been taken into account in multivariate analysis and does not modify the conclusions of the study.

[Slide]

A median of 6 and respectively before every 3-week cycles have been administered to the patients. You will notice that the range goes above 10 as the investigator felt it was in the patients' best interest to continue treatment in a few cases. This occurred for 5 patients on Taxotere and 2 on the comparator arm.

[Slide]

Cycle delay or reduction was rare, and balanced between the 2 arms. This fact translates into the high relative dose intensity on both arms.

As we expected, based on the Phase II data, the incidence of grade 3-4 neutropenia was higher on the

Taxotere arm. This explains the higher incidence of febrile neutropenia by both definitions of this adverse event, as you can observe here. Grade 3-4 infections were more frequent on Taxotere. Also expected was the more frequent incidence of thrombocytopenia in the MV arm.

[Slide]

The most common severe or NCI grade 3-4 non-hematologic toxicities are reported in this slide. These toxicities are usually rare and reflect the incidence previously reported for Taxotere and mitomycin C-vinblastine. They include allergy, nausea, vomiting, diarrhea, constipation, stomatitis, neurosensory, skin, nail disorder, asthenia and fluid retention.

[Slide]

The primary reason for treatment discontinuation as assessed by the investigator shows that more patients discontinued study the treatment due to progressive disease on the MV arm. Other reasons for treatment discontinuation, all depicted on the slide, were relatively well balanced. Details on the adverse experience leading to study withdrawal are provided on the next slide.

[Slide]

And, 5% of the patients went off study on the MV arm due to thrombocytopenia, and 5% due to neurotoxicity on the Taxotere arm. Only 3% of the Taxotere patients

discontinued due to fluid retention. A small percentage of MV patients discontinued due to constipation.

[Slide]

According to the assessment of the treating physician, 7 treatment-related deaths were reported. The 4 deaths associated with Taxotere occurred within 30 days of last treatment, while 2 of the deaths linked to MV occurred more than 30 days after the last infusion. Infection was the most common cause of death in the Taxotere group, while mitomycin C-related toxicities were the cause of death on the MV arm.

[Slide]

The patients who received Taxotere had a much higher response rate. A 30% response rate for Taxotere, compared to a 12% response rate for MV is statistically significant, with a p less than 0.001. While stable disease was similar on both arms, progression was much more frequent on the MC arm.

[Slide]

Time to progression was the primary endpoint of this study, and is clearly in favor of Taxotere. The 19 weeks compared to 11 weeks median time to progression difference is highly significant, both by log rank and Wilcoxon analysis.

[Slide]

Remarkably, in a study including heavily pretreated patients, who could also crossover to the comparator arm, survival was better for those patients under the Taxotere arm. It is important to notice that this translates into a 50% relative increase in probability of survival at 12 months for patients in the Taxotere arm as compared to the control arm. I would like to emphasize again that the multivariate analysis taking into account the previously discussed imbalances or prognostic factors among the 2 arms of the study has been conducted. This multivariate analysis shows that the advantage for treatment with Taxotere remains valid after correction for these factors.

[Slide]

While we accept that subgroup analyses are only of exploratory nature, we, nevertheless, show here that the difference in favor of Taxotere is presenting all prognostic subgroups, like visceral involvement, liver involvement, patients who had adjuvant prior treatment only, patients who had adjuvant and advance treatment, patients who were resistant and not resistant by definition in this study.

[Slide]

It is important to give some details about those patients who were not anthracylcine resistant. As you can see, the primary endpoint of the study, time to progression,

is in favor of Taxotere in this subset with 33 weeks versus 14 weeks, and the response rate is also in favor of Taxotere with 31% versus 18% of the patients responding. There is also a trend in favor of Taxotere with 14 versus 11 months for survival.

[Slide]

Quality of life data collection was performed with the EORTC QLQ questionnaire 30 at baseline, every second cycle, at end of study and every 3 months thereafter. Collection was to be performed after progression or further anti-cancer treatment. Compliance with these particular requirements was comparable on both arms. However, attrition, that is, the cumulative proportion of patients off quality of life analysis, was higher on MV, as predicted on the next slide.

[Slide]

This graph represents the cumulative percent of patients who went off the quality of life study among patients who completed the quality of life forms at baseline. The reason not to continue the quality of life data collection was progressive disease, adverse events, patients refusal or death. As you can see, many more forms are missing on the MV arm for these reasons, which can all have a negative impact on quality of life evaluation. This non-random attrition may mean that the deterioration of

patients condition due to disease progression is not well reflected in the presented quality of life data.

Within these limitations there was no difference between the 2 treatment groups for mean score global health status. As a frame of reference, the mean baseline quality of life scores for patients whose initial performance of status is 90 or more, or initial performance status is 80 or less are shown as straight horizontal lines on this graph.

[Slide]

There is no apparent difference between the 2 arms of this study in quality of life instrument terms. The interpretation of this apparent lack of difference is limited by the high attrition rate on MV, which did not occur at random but was due to negative factors like disease progression. These factors clearly would have had a negative impact on quality of life if they had been taken into account by the administration of the instrument following progressive disease or toxicity.

[Slide]

To conclude, study 304 showed that Taxotere is superior to MV in terms of higher response rate, 30% versus 12%, p less than 0.001; longer median time to progression, 19 versus 11 weeks, p less than 0.001 by log rank; longer median survival, 11.4 versus 8.7 months, p less than 0.01 by log rank. This result is achieved with a manageable safety

profile and comparable quality of life.

[Slide]

This prospective study in advanced breast cancer patients confirms the safety and efficacy of Taxotere in anthracylcine-resistant patients. This study provides further evidence for the activity of Taxotere in patients previously exposed to but not resistant to anthracyclines.

I would now like to call on Dr. John Crown, who is going to present study 303.

Study 303

DR. CROWN: Thank you, Dr. Aapro.

[Slide]

Members of the Oncology Drugs Advisory Committee, ladies and gentlemen, it is a great privilege for me to have the opportunity to present the results of the 303 study today. This was a randomized comparison of Taxotere versus doxorubicin in patients with metastatic breast cancer who had previously been treated with alkylator agent-containing chemotherapy.

I would like to take this opportunity to acknowledge the contributions of the many investigators who made this large-scale international trial possible. Our most profound gratitude goes to the 326 women, from 15 countries, who took part in this study.

[Slide]

The rationale for the study was that doxorubicin was generally regarded as being the most active chemotherapy drug then available for treatment of metastatic breast cancer. The use of doxorubicin is, however, associated with troublesome organ toxicities, including cardiac toxicity. As Taxotere had been shown to be highly active in single-arm studies in metastatic breast cancer, a randomized comparison of these drugs was felt to be required.

[Slide]

The primary endpoint of our study was time to progression from the date of randomization. Secondary endpoints included response rate, time to treatment failure, survival, safety and quality of life. All of our analyses were based on intention-to-treat for all randomized patients, including those who were not treated and those who were found to be ineligible following central protocol review.

[Slide]

The trial was a prospective, randomized, non-blinded comparison of Taxotere versus doxorubicin in patients with metastatic breast cancer and prior exposure to alkylator agent chemotherapy. Taxotere was administered at a dose of 100 mg/m^2 every 3 weeks as a 1-hour intravenous infusion. Steroid premedication was routinely given as prophylaxis against fluid retention. Doxorubicin was

administered at a dose of 75 mg/m^2 on an identical 3-week schedule as a short intravenous infusion, and with antiemetic as per local practice.

It was planned to give 7 cycles of treatment on both arms of the study due to the recognized risk of cardiac toxicity at higher cumulative doses of doxorubicin. There was a preplanned schedule of response evaluation after every 2 cycles, at the end of the study and every 3 months in the follow-up period.

[Slide]

Due to concerns about cardiac toxicity with doxorubicin, a left ventricular ejection fraction was performed prior to study in both arms, after a cumulative dose of 400 mg/m^2 and at the end of study in both arms. Treatment was discontinued for cardiac toxicity in the event that patients had a left ventricular ejection fraction which decreased by 10 absolute points if the decrease was also below the lower limit of normal. This is a recommendation which has been published by Schwartz. Of course, clinical heart failure was also specified as a reason for immediate treatment discontinuation.

[Slide]

In addition to the usual eligibility criteria of adequate organ function performance status, it is important to emphasize that all patients on the study had cancer which

had progressed following prior alkylator agent-containing chemotherapy. Prior anthracylcine or taxane chemotherapy were absolute exclusion criteria, and all patients had progressive metastatic disease at the time of study entry.

[Slide]

A total of 326 patients were randomized between July of 1994 and January of 1997. The cut-off for our analysis is September 15, 1997. A total of 99% of patients on both arms of the study received at least 1 cycle of therapy. The patients were well matched for age and for performance status, and for all other major clinical criteria. There were not statistically significant differences between the arms in pretreatment characteristics.

[Slide]

In this trial, patients were prospectively characterized as having either resistant or non-resistant disease. Resistant disease was defined as cancer which had relapsed while the patient was undergoing, or was within 12 months of completion of adjuvant therapy, or disease which had progressed within 30 days of prior chemotherapy for metastatic disease. Non-resistant cancer, on the other hand, was disease which progressed more than 30 days following a prior chemotherapy-induced response, or disease which had relapsed more than 12 months following completion

of prior adjuvant chemotherapy.

[Slide]

All patients on both arms of the study had received prior alkylator agent-containing chemotherapy. In some cases only in the adjuvant setting, some in the setting of metastatic disease, or some had received it in both settings. Approximately 51% of patients were randomized to receive Taxotere and 43% randomized to receive doxorubicin had received only adjuvant therapy. The remainder of the patients had received chemotherapy for advanced disease, with a small number having received chemotherapy in both clinical settings. And, 47% of patients who were randomized to Taxotere and 52% of patients who were randomized to doxorubicin had resistant disease. This difference was not statistically significant. On both arms, 17% had developed relapsed cancer within 12 months of completion of adjuvant chemotherapy; 30% and 34% of patients who were randomized to Taxotere and to doxorubicin respectively, and who had previously had chemotherapy for advanced disease relapsed within 30 days of that chemotherapy.

[Slide]

The patients had predominantly poor prognosis visceral disease. Approximately 43% of patients on both arms of the study had 3 or more organ systems involved with cancer. As you can see, the majority of patients had

bidimensionally measurable disease.

[Slide]

A total of 928 cycles of Taxotere and 832 cycles of doxorubicin were administered. The median number of cycles of chemotherapy received was 7 for Taxotere and 6 for doxorubicin. Please note that the range of cycle numbers for Taxotere extends to 11 cycles. This reflected the data from a total of 8 patients in whom the investigator clinician felt that it was in the patient's best interest to continue treatment beyond the protocol mandated 7 cycles. Treatment delay was more common on the doxorubicin arm, predominantly due to slow neutrophil recovery. Dose reductions occurred equally frequently on the 2 arms. The median relative dose intensity was approximately 25% in both arms of the study. It is important to note that this was calculated using the actual number of cycles delivered as the denominator.

Patients who were randomized to receive Taxotere received an average of 641 mg/m^2, for doxorubicin the figure was 435.

[Slide]

Severe neutropenia was common in both arms of this study. Febrile neutropenia, as defined by the occurrence of grade 3 or grade 4 neutropenia together with fever greater than 38 degrees, occurred approximately equally frequently

in both arms of the study. But the incidence of febrile neutropenia which required hospitalization and/or intravenous antibiotic therapy, as per the well-defined Pizzo criteria, was significantly higher with doxorubicin.

Documented sepsis was also significantly more common following doxorubicin therapy. A significantly higher percentage of patients experienced severe anemia and required red cell transfusions on doxorubicin arm.

The occurrence of thrombocytopenia and of severe grade 3 or grade 4 thrombocytopenia were both significantly more common on the doxorubicin arm.

[Slide]

Nausea, vomiting, stomatitis and, as we shall see in a few moments, cardiac toxicity were all significantly more common on the doxorubicin arm of the study, whereas diarrhea, neurosensory toxicity, nail toxicity and fluid retention, which we shall see more about in a moment, were more common on the Taxotere arm of the study. There was no significant difference in the incidence of severe skin toxicity, allergy or asthenia between the 2 arms.

[Slide]

While mild fluid retention was common, severe fluid retention only occurred in 5% of patients treated with Taxotere, and this necessitated treatment discontinuation in only 2% of patients who were treated with this drug. The

median cumulative dose to the onset of fluid retention was 478 mg/m^2.

[Slide]

Cardiac toxicity was a prominent problem on the doxorubicin arm of the study and 9% of patients had to be withdrawn from study due to cardiac toxicity; 4% had clinical cardiac failure; 2% of patients who received doxorubicin died from cardiac toxicity. It is important to note that these deaths and episodes of clinical heart failure which occurred, all occurred at cumulative doxorubicin doses less than 460 mg/m^2.

Decreased left ventricular ejection fraction was seen in 8% of patients treated with Taxotere and in 29% of those who received doxorubicin. However, severe decreases were only seen following doxorubicin, and affected 11% of patients so treated.

[Slide]

As can be seen in this slide, 46% of patients who were randomized to receive Taxotere and 34% of those randomized to receive doxorubicin received all 7 cycles of therapy. The reasons for treatment discontinuation, which are outlined in this slide, are those which were reported as assessed by the investigator as the primary reason for treatment discontinuation. A larger number of Taxotere patients received the full 7 cycles without the necessity of

treatment discontinuation due to progressive cancer, serious toxicity, withdrawal of consent, toxic death or for other reasons.

[Slide]

Nineteen patients who received Taxotere and 26 patients who received doxorubicin were withdrawn from the study due to an adverse event. The predominant treatment-related side effect which necessitated the discontinuation of doxorubicin therapy was cardiac. Neurologic toxicity and fluid retention were the most frequent adverse events which necessitated treatment discontinuation on the Taxotere arm.

[Slide]

In the opinion of the treating oncologists, two patients died on the Taxotere arm due to drug toxicity. Both died within one month of the last study treatment. Five patients on the doxorubicin arm died from reasons related to the study drug, and four of these deaths occurred more than one month after the last infusion. One patient died from infection in each arm of the study. One patient who was treated with Taxotere, with abnormal and rapidly deteriorating liver functions due to hepatic metastasis at baseline, died following the first cycle. A putative role for the drug could not be conclusively ruled out. The remainder of the toxic deaths on the study were complications of the cardiac toxicity or doxorubicin. I

should point out again that none of the patients who died from cardiac toxicity had received more than 460 mg/m^2.

[Slide]

This slide summarizes the response data. Complete response was seen in 7%, and in 4% of patients receiving Taxotere and doxorubicin respectively; partial response in 41% and 29% respectively. The overall response rates were 48% for Taxotere and 33% for doxorubicin, a difference which was highly statistically significant.

[Slide]

The primary endpoint of the study was time to progression from the date of randomization. The median time to progression was 26 weeks for Taxotere and 21 weeks for doxorubicin. There was a trend for an early advantage for Taxotere in terms of time to progression, reflected in the Wilcoxon test although, however, the difference between the 2 arms was not statistically significant.

[Slide]

Time to treatment failure was a preplanned statistical analysis in the protocol. Time to treatment failure was defined as the time from the date of randomization until progression of cancer, death for whatever reason, withdrawal from study due to an adverse event, patient refusal, loss to follow-up or further anti-cancer therapy which was administered before documentation

or progression of cancer, whichever came first.

The median time to treatment failure was 22 weeks for Taxotere versus 18 weeks for doxorubicin. This difference was significant according to the Wilcoxon test. The data are somewhat reminiscent of the data we just presented for time to progression in that the results are a lower incidence of earlier negative events in the Taxotere arm.

[Slide]

There was no difference in overall survival between the 2 arms. It is important to note in this regard that patients were allowed to receive any treatment at the time of progression, and approximately 50% of patients in both arms received further chemotherapy at the time of treatment failure. Approximately 30% in both arms, in fact, received either the other study drug or an analog of the other study drug at the time of progression.

The efficacy results just reported, response rate, time to progression, and survival, were confirmed in multivariate analysis showing that no slight imbalance in the patient population accounted for the statistically significant difference seen in the response rate, and confirmed the lack of a statistically significant difference in TTP and survival.

[Slide]

An analysis of response according to the most important prognostic factors for this endpoint showed the consistency of the response advantage for patients treated with Taxotere. For these categories, the response rate in the Taxotere group ranged from 44% to 54%, whereas in the doxorubicin group it ranged from a low of 15% to 49%.

These subset analyses are presented only to demonstrate that the overall response rate reflects not just the data from one subpopulation. As can be seen, in fact, the greater impact of Taxotere relative to doxorubicin is seen in the worst prognostic groups, e.g., those with hepatic metastatic disease or resistant disease.

[Slide]

In this study, quality of life data were collected using the EORTC QLQ-C30 which has 15 dimensions. Assessments were collected prior to therapy, after each of the 7 cycles and every 3 months thereafter until disease progression. Compliance with these requirements was comparable in both arms. Attrition, i.e., the cumulative proportion of patients off the quality of life analysis, was higher on doxorubicin.

[Slide]

This graph represents the cumulative percent of patients who went off the quality of life study among patients who completed quality of life forms at baseline.

The reasons not to continue the quality of life data collection were progression disease, a serious adverse event, patient refusal or death. Many more forms are missing on the doxorubicin arm for these reasons. This non-random attrition resulted in the loss of data from a higher number of patients on the doxorubicin arm who suffered negative events, i.e., toxicity, and progressive cancer, which are known to be associated with the deterioration and quality of life. This may mean that our study design did not allow the accurate representation of the deterioration of patient condition due to the disease progression and toxicity. This limitation should be kept in mind when reviewing the longitudinal changes and global health status which are depicted in the following slide.

[Slide]

As a frame of reference, the mean quality of life scores for patients with an initial performance status of 90-100 and of 60-80 are shown on the figure by the straight horizontal lines. The lines with the vertical arrow bars represent the global health status scores at each time point.

You will note from the figure that the baseline scores are higher in the women randomized to the Taxotere treatment. This difference is statistically significant but small relative to the clinically meaningful differences

indicated by the reference lines. The differences between the 2 arms disappear over time. However, when comparisons with respect to the baseline are made, the differences after cycle 4 and after cycle 6 are statistically different but represent small effects which are unlikely to be clinically meaningful.

[Slide]

Three out of four patients on the study did not experience a clinically meaningful deterioration in their performance status while on study. This slide describes the time to deterioration by more than 20 points of the Karnofsky scale. As you can see, there was no disparity in rate of decline between the 2 arms.

[Slide]

In conclusion, in comparison to doxorubicin, Taxotere demonstrated a statistically significantly higher response rate; a longer median time to progression; a statistically significantly longer median time to treatment failure, 22 versus 18 weeks; and a comparable median survival.

[Slide]

These 2 agents, however, showed very different toxicity profiles. Doxorubicin produced significantly more frequent and more severe thrombocytopenia; more frequent anemia; and a higher requirement for red blood cell

transfusions; documented infection; febrile neutropenia which necessitated hospitalization or intravenous antibiotics; more frequent nausea, vomiting, stomatitis; and more frequent cardiac toxicity which was sometimes fatal in the doxorubicin arm.

Taxotere, on the other hand, produced more frequent diarrhea, neurological toxicity, skin toxicity, and a fluid retention syndrome which was generally mild. Taxotere is a safety and efficacy treatment for patients with metastatic breast cancer after the failure of alkylator agent-containing chemotherapy.

Thank you very much. I would like to hand you back to Dr. Kathy Pritchard.

Discussion

DR. PRITCHARD: Thank you, Dr. Crown.

[Slide]

Once again, I would like to try to put into perspective the data that you have seen over the last two presentation.

[Slide]

Firstly, in relation to the TAX 304 data, it has been unclear what were the best options following relapse after anthracylcine adjuvant therapy, or after progression following anthracylcine therapy for metastatic breast cancer. Up until this time there has been an extremely

limited number of Phase III trials in women whose tumors have progressed following anthracylcine therapy.

[Slide]

The two major randomized study comparisons are shown on this slide, TAX 304, which you have just heard presented, and Stephen Jones' study, published in JCO in 1995, comparing weekly venorelbine to intravenous melphalan given every 4 weeks.

As you can see in the melphalan versus venorelbine study, the response rates are low, and the improvement in time to progression and survival, although statistically significant, are relatively small, while in TAX 304 the response rate is higher for Taxotere, and the improvements in time to progression and survival are somewhat more substantial.

[Slide]

One must, of course, interpret these results with caution as they do represent cross-study comparisons in a heterogeneous patient population. Nonetheless, Taxotere has certainly shown superior efficacy, including prolonged survival, in comparison to mitomycin C and vinblastine. It's safety profile, given at 100 mg/m^2 every 3 weeks, is acceptable and should be considered a primary option for patients with metastatic breast cancer, following treatment with an anthracylcine.

[Slide]

For women who have had and relapsed following, or progressed while on an alkylator agent combination, such as CMF, anthracylcine has been the standard therapy, as I mentioned earlier. Studies comparing doxorubicin as a single agent to a variety of other agents have been carried out.

I think it is useful to look at these studies to show two points. In the EORTC and inter-group studies none of the patients had received prior chemotherapy for advanced disease, and only about 30% had even received prior chemotherapy in the adjuvant setting in comparison to over 40% in the TAX 303 study.

[Slide]

The second point is that looking at all four trials together, it is only in the TAX 303 randomized trial that the comparator, Taxotere in this case, shows a significantly increased response rate in comparison to doxorubicin. Taxotere's safety profile was different, but also favorable in comparison to doxorubicin's.

[Slide]

I would like to make three points in showing this slide. First, a comparison of doxorubicin 60 mg to 75 mg in the EORTC and in the TAX 303 study shows comparable toxicity in all recorded doxorubicin-related categories, which are

infection, congestive heart failure and toxic deaths.

Second, comparing the doxorubicin 75 mg/m^2 dose between the EORTC and the TAX 303 arms, all toxicity categories are extremely similar.

Third, and perhaps most important, five of the most debilitating and dangerous toxicities, febrile neutropenia, at least as measured by the Pizzo criteria, severe infection, vomiting, stomatitis and congestive heart failure are all significantly lower in the Taxotere arm.

[Slide]

In summary, Taxotere in comparison to doxorubicin 75 mg/m^2 has at least comparable anti-tumor efficacy, and a toxicity profile which is both different and favorable in terms of several important limiting toxicities of doxorubicin. Thus, I believe that Taxotere offers an important option to women and physicians in this setting.

Now I would like to introduce Dr. Philip Chaikin, who will make some further conclusions.

Conclusions

[Slide]

DR. CHAIKIN: I would now like to make some concluding remarks to complete the information in support of this application.

[Slide]

We believe that the two adequate and well-

controlled studies presented here today provide further information to verify and describe the clinical benefit of Taxotere. The objective of this s-NDA are shown on this slide.

TAX 304 demonstrates the superior activity of Taxotere in patients whose disease is anthracylcine-resistant. This is the study population included in the currently approved labeling based upon Phase II data. This study supports the approval for Taxotere from accelerated to full.

In addition, TAX 304 demonstrated that Taxotere has superior activity versus an active treatment in patients previously exposed to an anthracylcine-containing regimen. This study, along with study TAX 303 which evaluated patients previously exposed to an alkylator agent-containing regimen, supports the expansion of the indication for Taxotere to patients whose disease has progressed following previous chemotherapy.

An additional requirement for full approval is the confirmation of the safety results as incorporated in the package insert at the time of accelerated approval. The updated integrated safety summary, which now includes more than 2000 patients treated with Taxotere at 100 mg/m^2, shows a profile entirely consistent with the results previously reported.

[Slide]

There has been no significant difference observed between the safety profile described in the U.S. package insert, including 1435 patients at the time of accelerated approval, and that reported in the updated integrated safety summary provided with this supplemental NDA, which includes 2045 patients. These results in 610 additional patients are, for the most part, from breast cancer patients and multicentered Phase II and III studies.

[Slide]

In the next three slides, I will review the updated integrated safety summary compared to the 1996 package insert. These slides provide the results for all patients treated at 100 mg/m^2 and, additionally, provide a column detailing the safety results for patients with breast cancer.

Severe hematologic toxicity, shown on this slide, including grade 4 neutropenia, febrile neutropenia, severe infections and toxic deaths, was remarkably consistent and has not changed with additional Phase II and Phase III experience.

[Slide]

As seen on this slide, the incidence of all severe non-hematologic toxicities continues to remain low. This includes allergy, nausea, vomiting, diarrhea, stomatitis and

myalgia. The incidence of allergy is reported here in those patients treated with corticosteroids and has remained stable.

Additional severe non-hematologic toxicity, shown on this slide, such as neurosensory, skin, nail toxicity, asthenia and fluid retention, have remained low and stable. In particular, the incidence of severe fluid retention with corticosteroids remedication has remained stable.

Having confirmed that the safety profile of has Taxotere has not changed since the accelerated approval in May of 1996, and continues to be predictable and manageable, I will now quickly recap results which demonstrate the efficacy of Taxotere in the two randomized Phase III studies presented here today.

[Slide]

TAX 304 demonstrated the benefit of Taxotere by providing a significantly greater response rate and longer time to progression and survival, with a manageable safety profile in metastatic breast cancer patients after anthracyclines have failed. To our knowledge, this is the largest Phase III study conducted in this patient population, and the only trial demonstrating such an advantage.

[Slide]

It is important to note that in study 304 44% of

the patients are non-anthracylcine resistant. In this subset population the median time to progression and response rate is in favor of Taxotere versus mitomycin C and vinblastine. Therefore, TAX 304 provides further evidence for the activity of Taxotere which supports the expansion of the current labeling to include patients previously exposed to an anthracylcine-containing regimen.

[Slide]

TAX 303 showed the benefit of Taxotere over doxorubicin in demonstrating a statistically significant increase in response rate and time to treatment failure, and a trend for an earlier advantage in median time to progression, although overall not statistically significant. There was no difference in survival but, as Drs. Crown and Pritchard have already pointed out, the improvement in response rate, time to progression, and time to treatment failure, combined with a more favorable safety profile compared to doxorubicin, provides an important clinical benefit for the patient.

[Slide]

Because of the positive results in these two studies, conducted in populations previously treated with standard chemotherapy regimens for breast cancer, we believe that the proposed indication for this supplemental NDA is justified, which states that Taxotere for injection

concentrate is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of previous chemotherapy.

Finally, I would like to recognize the many investigators and patients that made these studies possible and meaningful. That concludes our presentation. We will now be pleased to answer any questions that you may have. I would like to thank you all very much for your attention.

Questions from the Committee

DR. DUTCHER: Thank you. Questions for the sponsor from the Committee? Dr. Margolin?

DR. MARGOLIN: Can you tell us whether the 6% incidence of severe infections included opportunistic or fungal infections in this population, who is averaging, by my calculations, 4 mg of Dupuytren a day throughout 7 treatment cycles, or 6, depending on which study?

DR. CROWN: No, this reflected more serious actual septic episodes with positive cultures.

DR. MARGOLIN: So, for some reason, despite all the steroids, we are not seeing opportunistic infections in these patients?

DR. RIVA: No, we have not seen any opportunistic infection, just gram-negative and gram-positive by culture. I am Alessandro Riva.

DR. SCHILSKY: I have a few questions. Can you

just comment a little bit further with respect to the duration of grade 3 and 4 neutropenia, as well as the duration of diarrhea in the patients on the Taxotere arm?

DR. RIVA: The duration of grade 4 neutropenia on the Taxotere arm is very short. First of all, it appears around day 7, day 8, and the grade 4 neutropenia disappeared around day 10, day 11. On the other hand, in TAX 303, where we have also checked the blood count for doxorubicin, the nadir on doxorubicin appears on day 14. So, it is a little bit later in comparison to Taxotere. Also, it lasts a little bit longer because we have more patients in the doxorubicin group who, at day 21, plus 1/minus 3, were not able to continue the next administration and delayed the next administration due to failure of recovery.

DR. SCHILSKY: Could you also just briefly review for us again how the severity of fluid retention was graded? What is severe fluid retention?

DR. RIVA: As you know, the NCI criteria do not plan for criteria to detect fluid retention. So, we developed a scale to follow fluid retention, and we have a slide to show this.

[Slide]

So, we have developed the following fluid retention scale, mild, moderate and severe. The patients were classified as having mild fluid retention if they did

not have any symptomatic fluid retention, asymptomatic or very well tolerated fluid retention, of asymptomatic infusion without any intervention required. In the moderate, you find moderate function impairment and well tolerated and/or dependent throughout the day. As far as infusion is concerned, in the moderate we had symptomatic fluid retention, exertional dyspnea and/or chest pain and ECG changes in the case of pericardial infusion, and lower abdominal distention. The other criteria are severe.

I would like to point out that very few patients in both studies developed pleural effusion or pericardial effusion, despite the fact that median cumulative dose of Taxotere was very high, 600 mg/m^2. These criteria were developed and prospectively defined in both protocols, and actually these are the criteria that we are following for all the Taxotere protocols and also in adjuvant treatment.

DR. SCHILSKY: So, how is the fluid retention generally managed when it occurs?

DR. RIVA: The protocol makes one statement. Normally, we suggest to manage with diuretics. However, we left the decision of the investigator for the best way to manage fluid retention. I would like to call on John Crown.

DR. CROWN: Well, fluid retention is managed in a number of different ways. I guess one of the most important interventions is really just a little bit of patience

because it does tend to get better with the passage of time. Obviously, there have been attempts to treat it with diuretics, which have had various and generally not terribly spectacular degrees of success. But, in truth, it is now with the prophylaxis schedule seldom a major problem actually requiring very active therapeutic intervention, other than reassurance that it will clear up.

DR. SCHILSKY: I have another question on a different topic. Can you tell us what percentage of patients in both studies actually had steroid hormone receptor positive tumors, and what percent of patients had prior hormone therapy?

DR. LEVI: In terms of TAX 303, we had around 50% of patients with estrogen positive, but, unfortunately, for 30% of the patients we were not able to have this information because these are metastatic breast cancer patients and it is at times difficult to obtain the data. This is the same pattern seen in TAX 304, although a little bit lower. The patients with estrogen positive were around 40%.

In terms of the treatment of adjuvant therapy, I can show a slide for the two studies. The patients were balanced in terms of prior adjuvant chemotherapy.

[Slide]

So, the two groups were balanced for prior

adjuvant therapy and advanced mono-therapy for both studies.

[Slide]

Here you have the slide summarizing TAX 303. Here you have 70% of the patients on Taxotere who received hormonal therapy and 70% on the doxorubicin arm received hormonal therapy.

[Slide]

You can also see the intent of prior hormonal therapy. You can see that 35% of the patients on the Taxotere arm received hormonal therapy for adjuvant intent, and 26% on the doxorubicin arm. It is interesting to see that you have comparable numbers for the patients receiving adjuvant therapy for advanced disease.

[Slide]

The same trend is observed for TAX 304. So you see that the patient categories are quite balanced. The intent is 66% of patients on the Taxotere arm, and 60% of patients on the mitomycin-vinblastine arm received prior adjuvant hormonal therapy.

DR. SCHILSKY: I guess I bring it up only because I suppose one could make the argument that patients on the Taxotere arm received chemotherapy plus a hormonal therapy, whereas patients on the comparator arm received chemotherapy therapy without hormonal intervention.

DR. AAPRO: You are absolutely right. This could be potentially a problem. However, the patients also on the other arm, because of the present usage of antiemetics with corticosteroids, also received corticosteroids, albeit a smaller dose. They also received corticosteroids. I think we are all aware of the U.K. data which showed in some patients with use of prednisone, it could have an influence. But 40% of the patients on the other arm also received corticosteroids.

DR. LEVI: I would also like to remind you that there is a paper just published by Diortisi. They compare Taxotere without corticosteroids versus Taxotere with corticosteroids. They used a 3-day regimen in metastatic breast cancer in those exposed to previous anthracylcine-containing regimen, and they didn't see any difference in the response rate in terms of time to progression.

DR. MARGOLIN: Since we don't have a lot of controversial questions, would someone mind spending a minute just explaining to those of us who don't know the mechanism of fluid retention with Taxotere, and how the high dose of corticosteroid is supposed to ameliorate that?

DR. LEVI: It is very difficult, as you know. It is very difficult to study the physiopathology of fluid retention because, actually, in the preclinical setting it is very difficult to find a model which is sensitive and

sensible enough to study this toxicity. However, we have conducted one study, in fact, in breast cancer patients not treated with corticosteroids. At the end of this study the conclusion of the experience was that this probably is related to capillary hyperpermeability related to the lieration of some cytokines during the administration of Taxotere.

So, behind this explanation you can also see the role of corticosteroids. If the corticosteroids is the best or not the best therapy today, we are not sure. Certainly, we are sure it works at least in the management of this syndrome.

DR. DUTCHER: Dr. Burris wants to make a comment.

DR. BURRIS: Burris, National, Tennessee. Just speaking as an American investigator, not having participated in these two trials but having participated in a number of the Taxotere studies, and also treating a number of patients off trial, I think the fluid retention, by and large, has become almost a case report phenomenon, with the nurses looking for it. I think, by an large, in treating patients now with the agent off study, just treating them ad hoc, it in fact becomes a very insignificant event, usually occurring in the range of probably 1/20 to 1/25 patients. So, I think clearly to say that severe fluid retention would cause discontinuation falling in that 3%, 4% range is

certainly an accurate reflection. Certainly, within the first 6 or 7 cycles, not a problem. Continuing patients past 6 or 7 cycles, I would estimate probably 1/10, 1/15 patients picking up some sort of symptom from it.

DR. LAMBORN: I guess this question has to be asked at some point. For 303, your sample statement states a hypothesis that there is an improvement over the control arm and, yet, obviously at this point you are saying that you have equivalence to the control arm in efficacy, with potentially improvement in safety. Does this really represent a change in thinking as a result of the data, or how did we move from one goal to ultimately the way you are now presenting the data?

DR. DURRLEMAN: I am Sylvan Durrleman, from Biostatistics. First, I would like to have the slide on time to progression for TAX 303 so that we can discuss it.

Indeed, this trial was designed as a superiority trial, with time to progression as the primary endpoint. We were looking for superiority of the Taxotere arm versus the comparator by 2 months in time to progression.

[Slide]

Obviously, as you have seen on the slide, we have been disappointed with the results that we observe here, knowing that we have a very high, substantially higher response rate, which is highly statistically significant as

compared to the control.

What you can observe on this curve, however, is that the assumption of proportional hazards seems questionable, at least on this slide. So, despite the fact that the primary endpoint or primary test showed a p value f 0.05, we thought that it would provide further insight into the phenomenon to provide also the results of the Wilcoxon test, which carries more weight for the early events. Indeed, there is a suggestion from the Wilcoxon test that something is going on.

Obviously, neither of those tests is very appropriate when the proportional hazards assumption does not hold. There is another test that is used in those cases, developed by Tom Fleming and Harrington a few years ago, which is the Kopmogonov-Smirnov test which actually tends to look at the difference between curves to see whether at some point there is a difference which is not random. This test, for your information, has a p value of 0.06, still not significant.

[Slide]

The next thing you would like to do, instead of simply surmising the results of such a trial by a p value, is also to look at some estimates of the magnitude of the effect that you observe. This is what we did, which is reflected in the statistical review of the FDA, on page 6 of

the statistical review, where you will see a table with the confidence interval for hazard ratios. The hazard ratio is close to 1, as you can see because the curves are really close. However, the confidence intervals are very narrow.

I think for many statisticians the lower bound of this confidence interval would suggest that there is, indeed, equivalence, although the sponsor does not claim that there is equivalence. We simply say we are certainly not inferior by a clinically meaningful difference in TTP. Does that answer your question?

DR. SCHILSKY: Let me just ask one other question about progression. Could you define for us, or could you give us the definition of progression that was used in these analyses, and also describe how progression was verified?

DR. LEVI: The definition of progression was according to the WHO criteria. So, the patient had to have an increase of 25% of the tumor, defined as a bidimensional measurable lesion at baseline, and the estimation of 25% more in a patient with evaluable disease.

It has to be noted also that if a patient had only 1 lesion which increased more than 25%, we considered this patient as progression.

DR. SCHILSKY: You had an independent review team, did you not, that looked at the patients who were considered to be progressing by the investigators?

DR. LEVI: In TAX 303, Taxotere versus doxorubicin, we saw 50% of the patients. Actually, we wanted to review all the patients with a chest x-ray or CT scan but, unfortunately, due to time constraints we were not able to review all the patients, in fact, because the investigators did not send us all the x-rays or CT scans. We did it anyway for this 50% of patients, and blinded response review, with one medical oncologist and two independent radiologists, who reviewed the instrument examination without knowing the treatment assignment. The data that you have seen today reflect this independent response review.

On the other hand, in TAX 304 we reviewed only 10% of the patients by very simple rules, where the definition of the response given by the investigator did not reflect the tumor assessment presented in the case or report form with the independent response review. The data that you have seen today reflect this 10% of patients.

DR. SCHILSKY: So, the TAX 303 data is sort of a mix of half the cases which were reviewed, in which case you used those response rates, and half which were not reviewed, in which case you used those response rates.

DR. LEVI: Exactly. For 50% of patients for the independent review we used the data of the panel. For the other 50% we used the data of the investigator. Actually, I

would like to add that there were not a lot of discrepancies.

DR. SCHILSKY: For those that were reviewed, what was the discordance rate?

DR. LEVI: It was less than 5% in both studies, in fact.

DR. OZOLS: In 303 there was no design crossover, but could you tell us a little bit more about what happened to patients when they progressed? I think about half of them received more chemotherapy.

DR. CROWN: On the 303, very close to 50% of patients on both arms of the study received further chemotherapy at the time of progression, and approximately 28% and 31% at the time of the crossover was unofficially to the other study drug or to an analog of the other study drug. We don't have response data for what happened when they had the their non-protocol unofficial crossover therapy.

DR. OZOLS: Did that relatively small amount who received additional therapy, 50%, when they progressed?

DR. CROWN: Well, I guess for many of the centers in many of the countries that were taking part in the study, the application of what would effectively be third-line chemotherapy or even fourth-line chemotherapy is some settings would not be considered absolutely standard.

[Slide]

DR. LEVI: I would like to add that there are also patients who received hormonal therapy and not chemotherapy. So, it is also important to take that into consideration.

[Slide]

The crossover was not planned into the protocol, but you see that among the Taxotere patients, 20% of patients received further doxorubicin and among the doxorubicin patients 23% received further Taxotere.

DR. LAMBORN: This may be in what you provided us but, if so, I have lost track of it. How many patients were censored for progression because they left the study without progressing, and then went on to the therapy? I think there were criteria whereby you censored them for progression if they left the study.

DR. LEVI: In fact, in the analysis for time to progression we censored the patients who received further chemotherapy before the progression, and we censored the patients at the last tumor assessment --

DR. LAMBORN: Yes.

[Slide]

DR. LEVI: So, as you can see here, we have very few patients that received further chemotherapy before progression, only 12 patients in the Taxotere arm and 7 patients in the doxorubicin arm. This table outlines the

reasons for censoring.

DR. LAMBORN: So, in fact, if I include because they had other therapy, they I have 22 in the Taxotere --

DR. LEVI: Correct.

DR. LAMBORN: -- and 92 in the doxorubicin.

DR. JONEA: I would like to add that we have done, obviously, sensitivity analysis to make sure that our results would not depend on those assumptions. So, in other words, we have done additional analyses considering the hose patients who took further chemotherapy as failures.

DR. LAMBORN: And the results when you did that?

DR. JONEA: The results are more positive for time to progression.

DR. TEMPLE: This is a question probably for the biostatisticians, and it is about study 303. I presume this isn't intended to be a trial that shows only an effect on response rate. You are also asserting that it showed an effect on a clinically meaningful endpoint, like time to progression. Had it shown superiority to the control agent, that would be self-evident because you can interpret a study like that. When a study fails to show a difference, however, you have more work to do. You have to establish that whatever difference between the therapies was ruled out represents an effect that is of a size that the active control actually had. So, you must have some theory,

knowledge, data on what the time to progression effect of doxorubicin in this setting is, otherwise you couldn't reach a conclusion about whether Taxotere has any effect. So, what sort of data do you have to do that? I mean, this has all been worked out and described by Tom Fleming and others.

DR. JONEA: As you know, unfortunately, the literature evaluating the effect of doxorubicin as a single agent versus the best supportive care in this particular setting is not wide. We do not have a lot of data. So, what we would need is to have some estimate of the effect of doxorubicin by itself, and then to make sure that with Taxotere we protect as much as possible this effect that we observe with doxorubicin. We now have some methods to do that, such as Baysian arguments based on confidence intervals. In this particular setting, unfortunately, given the scarce literature, we were not able to do that.

What we have done, however, is to look at the confidence interval for the odds ratio, and we say that the hazards ratio for Taxotere over doxorubicin, the upper limit of the confidence interval is 1.16. This is an unadjusted simple logarithm. We believe that many people would believe that this is really within the range of equivalence.

DR. TEMPLE: Why would many people believe that? Not that I wouldn't, but I am not burdened by any knowledge.

[Laughter]

Why would other people believe that?

DR. JONEA: I would say, you know, it is not a pure science; it is also an art and it depends on the experience. But I think most people who would design an equivalence trial in that setting would use hazard odds ratio, a maximum of, say, 1.25, and that would be considered as equivalence. So, we reach 1.16. So, I think we are well within.

DR. TEMPLE: So, people who believe that would believe that the effect of doxorubicin is at least 4 or 5 weeks, or something like that, on time to progression. I just did some rough calculations. That is 0.16 based on 20 weeks for doxorubicin. So, that is something like 4 weeks. Is that what you have to believe, that the time to progression effect of doxorubicin is about 4 weeks?

DR. JONEA: I think there is an important point to the design of that study that we have to keep in mind when looking at the time to progression as well, that given the cardiac toxicity of doxorubicin, the maximum number of infusions to be received in both arms was 7 infusions only. If you look at the time to progression survival curves in your binder, you will see that at that time, about 21 weeks, 22 weeks, the Taxotere curve starting to fall off, in other words, increasing at that time. So, there is a suggestion of speculation that if one were allowed to continue

treatment for those patients who are still in response you may see early improvement in TTP sustained.

DR. TEMPLE: But just to be sure, to believe that this study shows that there is an effect on time to progression you have to believe that the effect of doxorubicin is in the neighborhood of 4 or 5 weeks, and that you have excluded a difference worse than that. Is that the whole theory? Otherwise, all you have is response rate. You need some theory like that to have evidence of a clinical effect.

DR. LAMBORN: Where did you get the 4 to 5 weeks?

DR. TEMPLE: I made it up.

[Laughter]

That is 0.16 times 20, which is the median for doxorubicin, about 4 weeks. So, that is what the hazard ratio data excludes. If you exclude a difference of more than that, and you believe that doxorubicin had a 4-week effect, then you are home free.

DR. JONEA: I think that you are correct.

DR. DUTCHER: Are there any other vital questions for the sponsor? If not, we will take a 15-minute break.

[Brief recess]

DR. DUTCHER: We are going to proceed with the FDA presentation. Dr. Griebel is the reviewer.

FDA Presentation

[Slide]

DR. GRIEBEL: That wasn't anything as esoteric as having more than one presentation. I just shut off the computer, and I apologize. Mr. Gensinger is the last name on my list of acknowledgements, and I do thank him. These are the members of the team who worked on this application, this review.

[Slide]

Many of my slides are similar to what you have already seen. Taxotere was granted accelerated approval in May of 1996 for the indication for the treatment of patients with locally advanced and metastatic breast cancer whose disease has progressed during anthracylcine-based therapy of relapsed during anthracylcine-based adjuvant therapy.

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Under the regulations, accelerated approval is approval that is granted based on a certain endpoint. In this case, it was clinical response rates from Phase II studies. That approval is subject to a requirement that the applicant study the drug further to verify the clinical benefit and to describe that clinical benefit. And, as the sponsor remained committed to the completion of 4 Phase III studies, 2 of which are completed, TAX 303 and 304, and have been presented in this application. Two additional studies, TAX 311 and 313 are still under way.

[Slide]

This application's goals are two-fold. One is the conversion to full approval from accelerated approval. The second is to expand the labeled indication, basically dropping the anthracylcine wording from the current labeled indication to "for the treatment of patients with locally advanced or metastatic breast cancer whose disease has failed prior chemotherapy."

[Slide]

The patient populations in these two pivotal studies seem tailored to each one of these application goals. The TAX 304 patient population were patients who had been treated previously with a prior anthracylcine-containing regimen, and this patient population addresses the goal of the conversion from the accelerated to full approval.

The TAX 303 population have been treated with a prior alkylator-containing regimen, and this particular patient population seems best to address the expansion of the labeled indication.

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I am going to start with a discussion of the conversion from accelerated approval to full approval, and will focus first on TAX 304. TAX 304, as we have already heard, was a Phase III open-label, multicenter study, with

treatment arms Taxotere versus a combination of mitomycin C and vinblastine. Time to progression was the primary endpoint. Secondary endpoints included response rate and survival.

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The eligibility criteria included progressive metastatic disease and a history of prior anthracylcine exposure. Predefined in the protocol, that anthracylcine exposure could have been in a number of different settings. It could have been in the neoadjuvant setting as long as progressive disease had developed while receiving active neoadjuvant treatment with the anthracylcine. It could have been in the adjuvant setting as long as relapse occurred either while on active adjuvant treatment with an anthracylcine, or if the disease-free interval from completion of adjuvant therapy had been less or equal to 12 months. Or, relapse could have occurred greater than 12 months from adjuvant therapy, but as we have already heard, in that case there had to have been another first-line regimen given for advanced disease before the patient could be eligible for participation in TAX 304. Finally, the anthracylcine could have been given first-line for advanced disease. These different situations define the different anthracylcine-resistant categories which we have heard referred to, and I will be referring to later.

[Slide]

Primary resistant disease were these patients whose relapse had occurred while on active adjuvant therapy or had developed progressive disease as the best response for advanced disease. Secondary resistance was disease that relapsed within 12 months after adjuvant therapy, or in the treatment of advanced disease there had been some sort of response including stable disease followed then by progressive disease within 30 days after the last treatment with the anthracylcine. Finally, the not resistant category were those patients who had relapse greater than 12 months after adjuvant therapy, or had had some sort of response for advanced disease treatment including stable disease, followed then by progressive disease greater than 30 days after the last exposure to the anthracylcine treatment.

The protocol stated that the patient needed to have either/or measurable and/or evaluable disease. A patient could have evaluable only disease.

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The protocol specified that tumor assessments would be performed at cycles 3, 6, 8 and 10, with the exception being that bony disease did not have to be assessed at cycle 8.

Confirmation of response was to be performed at 28 days. The protocol stated that all sites of disease were to

be evaluated at each one of the cycles that were specified, and the baseline method of evaluation was to be carried through the entire study. Quality of life evaluation was to be performed essentially every other cycle. There was a post-study assessment period for patients who did not develop progressive disease on the active treatment phase of the study. After completion of therapy they would have assessment at 30 days, followed then by every 3 months.

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And, 392 patients were randomized on TAX 304, 387 patients were treated. In terms of the distribution between arms of the various resistance categories, there was equal distribution. As we have heard, approximately 45% of the patients on this study had disease that was considered not resistant to anthracylcine.

As far as the distribution between arms in terms of prior chemotherapy exposures, again, the 2 arms were similar.

Prognostic factors were similar, except for greater than or equal to 3-organ involvement, and this was higher on the control arm, 51.9%. Visceral involvement was similar.

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A median of 6 cycles of Taxotere was delivered on study, 4 cycles on the control arm. Dose reduction and dose

delay was more common on the Taxotere arm. The median relative dose intensity was 0.94 on Taxotere, the control, 0.99.

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In terms of my efficacy review, and I reviewed the tumor measurements and tumor assessments, the major concern that I had was that there wasn't strict protocol adherence among some investigators in the assessments that were performed. The primary endpoint in the study was time to progression, and the here were occasionally investigators who skipped assessments as outlined in the protocol. My concern for the primary endpoint was that if you skipped an assessment and came in later to the next specified protocol assessment and documented progressive disease at that point, I wondered if the assessment had been performed at the cycle where it was supposed to have been and was skipped, whether the progressive disease may have been documented then and perhaps we were seeing some falsely prolonged progressive disease time to progression.

In addition, there wasn't always protocol adherence to the 28-day confirmation of response. There might be long periods before another assessment was done and, unfortunately, when the assessment was done the patient had progressive disease. That raises the question of whether the confirmation of response had been done the

patient would have actually had response documented.

Finally, many of these patients had multiple tumor sites, and the here would be skipped sites in each evaluation and it would vary with sites to be skipped, and it left you sometimes with an uncomfortable feeling you were not being consistent in your response assignments when you had multiple data points that were being skipped from time to time.

Also, occasionally the baseline method of evaluation wasn't carried through the entire study period. Mainly, this was in terms of going back and forth between ultrasounds and CT scans.

[Slide]

There was reference in the application to an algorithm of response. I requested that. That was included in the TAX 303, 304 Phase III user dataset manual. Basically, this algorithm stated that if you looked at an assessment point, first you ruled out progressive disease. If you didn't see progressive disease, then you looked to see if each lesion had been assessed. If one lesion had not been assessed, that assessment point was to be considered not evaluable.

I went ahead and explored the issues that I have brought up using this algorithm. It did give you a sense that you were being very consistent in your approach to each

patient on each arm of the study.

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In terms of the response review, this ended up impacting on 14 Taxotere patients and 12 mitomycin-C-vinblastine patients. Basically, it took away 4 PRs from each arm of the study.

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Obviously, that dropped the response rate slightly in both arms. It dropped on the Taxotere arm from 30% down to 28.1% with the FDA review, and the drop in the control arm was from 11.6% to 9.5%. Despite those changes, it was still strongly significantly superior on the Taxotere arm.

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The primary endpoint was time to progression. I already mentioned my concern if you skipped an assessment and followed it with a progressive disease assessment, whether there may be false prolongation of time to progression.

To explore this, both in the on-study period active treatment phase of this study as well as the follow-up period, if an assessment point that was specified on the protocol was skipped and then the next assessment for progressive disease was documented, as an exploratory analysis I moved the progressive disease up to the time that the assessment was skipped. This impacted on 40 Taxotere

patients and 20 control patients.

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It dropped the time to progression on the Taxotere arm from 19 weeks to 17 weeks, and on the mitomycin C-vinblastine arm from 11 weeks to 10 weeks.

[Slide]

This is our graph of the Kaplan-Meier curve for time to progression of the sponsor data. The green line is the Taxotere arm and the red line is the control arm. If you freeze that in your mind and go to our curves --

[Slide]

-- they look very similar.

[Slide]

Looking at the time to progression on the table, even with the changes that were made, with the log rank analysis the p value is still significant in favor of the Taxotere arm. Very importantly in this study, as we have already heard discussed, the median survival on Taxotere was longer than the control arm and was statistically significant as well. I have already mentioned that even with our changes the response rate was significantly superior on the Taxotere arm.

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In terms of safety, Taxotere patients experienced more adverse events than the control patients, except in the

following categories: All grades of thrombocytopenia, all grades of vomiting. Grade 3-4 pulmonary events were somewhat higher and constipation was more common on the control arm.

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Grade 3-4 neutropenia was more common on the Taxotere arm. Overall, febrile neutropenia which was grade 2 or greater fever associated with grade 3-4 neutropenia had a greater incidence on the Taxotere arm. The Pizzo criteria which we heard defined earlier, the fever associated with grade 4 neutropenia, and that grade 4 neutropenia also associated with hospitalization and/or IV antibiotics was greater on the Taxotere arm, and overall infection had a greater incidence on the Taxotere arm.

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This is a list of grade 3 and 4 non-hematologic toxicities which were greater on the Taxotere arm as compared to the mitomycin C-vinblastine arm. Diarrhea was grade 3-4 and was greater. Stomatitis was actually grade 3 and was higher. Fluid retention, 8%. Neurosensory and neuromotor were both grade 3 and were higher, and skin toxicity.

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On my review of the submitted case report forms and the patient narratives from the sponsor, I ended up

increasing the deaths that I felt were at least possibly related to treatment by 3 patients on each arm, to 7 on the Taxotere arm and 6 on the mitomycin C-vinblastine arm.

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The 3 additional deaths that I considered at least possibly related to treatment with Taxotere are listed here. The first patient's death was attributed to cardiac arrest. They died on day 7, which is the most common day for a neutropenic nadir on Taxotere. Given the patient narrative, I thought that there was a paucity of data that was submitted and I thought there was a possibility that this could have been related to Taxotere.

This patient was very complicated. She died in cycle 2 but she had had problems since cycle 1. Her death was attributed to intra-abdominal sepsis. She had intra-abdominal carcinomatosis and her tumor did contribute to bowel obstruction and that made a very complicated picture for this patient. Finally, this patient died on day 8, again around the neutrophil nadir period on Taxotere,. Death was attributed to carcinomatous lymphangitis. She did have lymphangitic spread in her lungs at baseline. At the time of her death she presented with shortness of breath, a cough, sputum production, hemoptysis, a fever and neutropenia.

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So, does TAX 304 support the labeled indication for the treatment of patients with locally advanced or metastatic breast cancer whose disease has progressed ruing anthracylcine-based therapy, or they have relapsed during anthracylcine-based adjuvant therapy?

The primary endpoint, time to progression was statistically significantly superior on the Taxotere arm, and very importantly, median survival was superior on the Taxotere arm, and I have mentioned that the response rate was superior.

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These patients had all been treated with an anthracylcine. The response rate was lower than what was seen in the Phase II setting, but that is not unusual in a Phase III trial. As we discussed, almost 45% of the patients in this study had disease that was considered not resistant to anthracylcine.

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It was an open-label trial, and I did note some critical deviations that I have already discussed in terms of the tumor assessments, and there was an imbalance in the prognostic factor, that being number of organs involved with metastatic disease.

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Moving on to TAX 303, and application goals it

applies to, first of all, it was one of the studies the sponsor committed to for conversion from accelerated approval to full approval. As I mentioned, its patient population does seem tailored to the expansion of the labeled indication for the treatment of patients whose disease has failed prior chemotherapy, dropping the anthracylcine wording.

TAX 303 patient population had a history of treatment with one prior alkylator-containing regimen. It was a Phase III open-label, multicenter study. The treatment arms were Taxotere versus doxorubicin. Doxorubicin was dosed every 3 weeks at 75 mg/m^2, given as a short infusion. The arms were capped at 7 cycles, and that came to a cap on the doxorubicin of 525 mg/m^2.

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Time to progression was again the primary endpoint. Secondary endpoints included response rate, survival and quality of life.

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The eligibility criteria were progressive metastatic disease. Again, the prior alkylator-containing regimen could have been given in a number of settings, similar to what we discussed in TAX 304.

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Disease had to be measurable and/or evaluable.

You could have evaluable only disease on this study. The protocol stated assessments would be done at cycles 2, 4 and 7. Confirmation of response would be done at 28 days. A best response of no change could not be assigned unless 6 weeks had passed from the time of treatment. This was later relaxed by the sponsor to 5 weeks.

All sites of disease according to the protocol had to be assessed at each one of those cycles, and the baseline method was to be carried through from the beginning to the end.

Left ventricular ejection fraction was to be assessed at baseline and at the completion of the study on both arms, and on the doxorubicin arm there would be an additional evaluation after the patient had accumulated a dose of 400 mg/m^2, and quality of life evaluation was to be performed at each cycle.

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And, 326 patients were randomized and 322 patients were treated. In terms of the distribution of the intent of prior chemotherapy between arms, more patients on the Taxotere arm had received their treatment as adjuvant only. More patients on the doxorubicin arm had received their prior chemotherapy for advanced disease only, and more patients on the doxorubicin arm had received both adjuvant and advanced chemotherapy.

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In terms of the distribution of different resistance patterns for the tumors between the two arms, more patients on the doxorubicin arm had primary resistant disease. More patients on the Taxotere arm had disease which was considered not resistant. Basically, half the patients on the study had disease which was considered not resistant.

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There was a longer time from last chemotherapy to randomization on the Taxotere arm.

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In terms of the distribution of prognostic factors, greater than or equal to 3-organ involvement was similar. Soft tissue only, which is a more favorable prognostic factor, was somewhat higher on the Taxotere arm. However, visceral disease only, which is poor prognostically, was higher on the Taxotere arm, but if you looked at any visceral involvement at all it was equal between arms. Bone involvement was more common on the doxorubicin arm.

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Again, just to quickly reinforce the difference in the prognostic factors, there were fewer doxorubicin patients who had non-resistant disease, more primary

resistant, more bone involvement. Taxotere, more not resistant, fewer primary resistant, more soft tissue only but more visceral only disease. There was a shorter time between last chemotherapy and randomization on the doxorubicin arm, and more patients with evaluable only disease. In an open-label study this could play into the hands of someone who is biased, but it could work both ways.

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Taxotere has a greater time between last chemotherapy and randomization, and there were fewer patients with evaluable only disease.

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The median number of cycles delivered on Taxotere was 7, and it was 6 on doxorubicin. Dose reduction by patient analysis was similar between arms, but in terms of dose delay by patient it was much more common on the doxorubicin arm. For doxorubicin, this is usually for hematologic toxicity. You say delays caused by both non-hematologic toxicity and hematologic toxicity on the Taxotere arm. The median relative dose intensity was 0.97 on Taxotere and 0.95 on doxorubicin.

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The same issues came up again in this trial in terms especially of not all the sites being assessed at each protocol-defined assessment point, and the method of

evaluation wasn't always carried from baseline on through the completion of the study.

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Again, to explore the impact of this I used the algorithm of response that I discussed earlier, and in doing this there was an impact on 6 Taxotere patients and 9 doxorubicin patients. This dropped the PRs on the Taxotere arm by 4 and dropped the PRs on the doxorubicin arm by 6. So, of course, you saw a decrease in response rate in both arms, but a little bit more so on the doxorubicin arm. The response rate on Taxotere dropped from 47.8% to 45.3% in the FDA analysis, and dropped from 33.3% to 29.7% on the FDA analysis. Despite these changes, there was a statistically significant difference between arms and it was superior on the Taxotere arm.

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The primary endpoint was time to progression, and although it appeared longer on the Taxotere arm this was not found to be statistically significant, with a p value of 0.45. The risk ratio or hazard ratio of Taxotere compared to doxorubicin on an unadjusted analysis was 0.93, and the confidence intervals are listed here, 0.71 to 1.16.

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Median survival was 14.7 months on Taxotere and 14.3 months on doxorubicin. The p value was again not

significant, 0.39. The risk ratio, again comparing Taxotere to doxorubicin, was 0.89. The confidence interval was 0.68 to 1.16.

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Just to reiterate, even with the changes that I made with the response rates, the FDA analysis showed that the response rate was significantly superior on the Taxotere arm, with a p value chi square of 0.004.

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So, we have superiority in response rate. Does that translate into clinical benefit? There are a couple of ways to look at. You can compare safety between arms, and you can also look to see if that response rate translates into quality of life for patients.

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I am going to start with the safety issues. Neutropenia was slightly higher on the Taxotere arm, grade 3-4 neutropenia. However, grade 3-4 anemia and thrombocytopenia were more common on the doxorubicin arm.

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Overall infection was slightly higher on the Taxotere arm. However, when you compare grade 3-4 infection there are actually slightly higher grade 3 infections on the d arm. Febrile neutropenia was similar, slightly higher on the Taxotere arm. When you split out that group that was

grade 4 associated as well with hospitalization and/or IV antibiotics, it was higher on the doxorubicin arm.

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Comparing all grades of non-hematologic toxicity and looking at the ones which were statistically significant and higher in incidence on the Taxotere arm, you find diarrhea, neurosensory, neuromotor, skin, allergy and pulmonary events.

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Stomatitis overall appeared higher on the doxorubicin arm but wasn't found to be statistically significant. Vomiting overall and overall nausea was, and it was significantly higher on the doxorubicin arm.

Cardiac toxicity was higher when evaluated by Schwartz criteria, which has already been defined as a 10% drop in absolute LV ejection fraction, also dropping below the limit of normal for the institution. These percentages that are listed here are actually the percentages of the patients who were evaluable for Schwartz criteria. There were 85 such patients on the Taxotere arm and 101 on the doxorubicin arm.

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Twenty-nine patients on the doxorubicin arm met Schwartz criteria, and 15 patients on doxorubicin had treatment discontinued because of cardiac toxicity. Three

of those patients were not evaluable for Schwartz criteria. Five patients developed congestive heart failure. In addition, the here was another patient who did not have a significant change in LV ejection fraction while on study but developed subsequent congestive heart failure, and 3 of these patients did die of congestive heart failure.

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All 3 cardiac deaths occurred at a cumulative dose of less than 450 mg/m^2, and CHF had occurred at a range of 375-457 mg/m^2.

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Again, going over the case report, the sponsor submitted narratives on the patients who died during treatment. I ended up increasing again the deaths which possibly could have been related to treatment with study drug. I increased it by 3 patients on the Taxotere arm and by 1 patient on the doxorubicin arm. This arm does include those patients who died of congestive heart failure.

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The 3 additional deaths attributed to Taxotere included this patient, who died in cycle 7 on day 14. Death was attributed to disease progression based partially on autopsy which was signed out as malignant pericardial effusion. This patient did have a baseline pericardial effusion, but because of the late onset of fluid retention

syndrome, and because this patient had gone to cycle 7 and had, in fact, gained weight, and I did not have a cytology to confirm that this was a malignant effusion I went ahead and attributed it possibly to the treatment with study drug.

This patient died in cycle 1 with an autopsy signed out as enterocolitis infection, and this patient died in cycle 1, around the time of expected neutropenic nadir. Death was attributed to pulmonary embolus. I went ahead and said this was possibly related to Taxotere because of the timing and because this death occurred in the home, and it appeared to me the that the diagnosis of PE was based on a history taken from the family.

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Moving on to quality of life, quality of life was a secondary endpoint in this study. It was assessed at each cycle. Prospectively defined endpoints to be assessed in quality of life by the sponsor focused on physical functioning and global health status, the first 5 questions on the questionnaire and the last 2.

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The primary endpoint was to focus on the global health score and to look for changes in the score at cycles 4 and 6 compared to baseline, and to look at time to worsening of global health status by 1 point and by 2 points. A secondary endpoint was physical function scores,

looking for changes from baseline at cycles 4 and 6.

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Compliance was good when you consider that this study capped at cycle 7 and at cycle 6 you still had 80.9% compliance on the Taxotere arm and almost 74% on the doxorubicin arm.

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In terms of changes in mean global health scores, and to put this into some perspective these global health scores were normalized to a 100-level scale, 0-100. So, if you look at cycle 4, there was a deterioration of 5 points on Taxotere and 9.6 points on Taxotere at cycle 6. On d there was an improvement of 2.5 points at cycle 4, and a deterioration of minus 0.8 at cycle 6. When these were compared to each other, they were statistically significant but you have to remember that they were normalized. These points were normalized to a 100-point scale.

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Similarly, with the physical functional scores, these were mean scores again compared to baseline, again normalized to a 100-level scale. At cycle 4 there was a deterioration of minus 7.5 on the Taxotere arm, a deterioration of minus 14 on cycle 6. Cycle 4 on doxorubicin, minus 1.9, 0 at cycle 6. Again, the differences were statistically significant.

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The FDA did an exploratory longitudinal analysis on the global health status scores. To explain this graph, the X axis are the cycles, going out to cycle 7. The green line is doxorubicin, and those are all doxorubicin patients. The top red line are Taxotere patients who completed the 7 cycles of therapy. The pink line are the Taxotere patients who only completed out to 3 cycles. These were separated out from one another because there was an apparent difference in behavior of these patients. As you see, this line appears fairly stable and you start to see a drop-off here on the completers.

The sponsor already mentioned that the baseline of doxorubicin on the global health status scores was statistically significant lower than the Taxotere scores.

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So, does TAX 303 support the proposed expanded indication, "for the treatment of patients with locally advanced or metastatic breast cancer who have failed previous chemotherapy?"

Well, all these patients had been treated with a previous alkylator-containing regimen. A third of the patients on the study had first-line treatment of disease that was considered not resistant.

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The response rate was significantly higher in the Taxotere arm as compared to the doxorubicin arm. There was an imbalance of prognostic factors between arms, and it was an open-label study, and there were some protocol deviations in tumor assessments.

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There was no statistically significant difference found between arms in the primary endpoint of time to progression or median survival. Quality of life improvement was not demonstrated with Taxotere treatment. We did find that there was a difference in the toxicity profiles between the 2 study drugs. In particular, there is less cardiac toxicity with treatment with Taxotere than with doxorubicin.

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To quickly summarize the application goals in the two pivotal studies, TAX 304 seems best targeted at the conversion from accelerated approval to full approval. There were patients who had previously been treated with anthracylcine, and there was found to be a significantly superior time to progression on the Taxotere arm and, very importantly, a superior median survival on the Taxotere arm.

TAX 303 had a population that seemed best targeted at the expansion of the labeled indication to having failed previous chemotherapy. These patients had been previously

treated with alkylating regimen and we did see a statistically significant significantly higher response rate on the Taxotere arm. There was no significant impact, however, going along with that response rate in time to progression or in median survival. But we did see a different toxicity profile. Despite the higher response rate, we did not see prolongation of time to progression or survival that was statistically significant and, importantly, we did not see a quality of life improvement that went along with the higher response rate.

I would be happy to take questions.

Questions from the Committee

DR. DUTCHER: Questions from the Committee for FDA? Dr. Margolin?

DR. MARGOLIN: You pointed out as a potential problem, at least in terms of our enthusiasm about this, that half of the patients in the TAX 304 study were not resistant by the definitions for anthracylcine-based therapy, but what we don't know is how much room did those patients have left on anthracylcine-based therapy, if they had been put back, say, on doxorubicin.

DR. GRIEBEL: I am trying to think. A lot of those patients, if I recall correctly, had failed or had gone greater than 30 days after advanced treatment. So, they were treated for advanced disease and then had their

progression occur greater than 30 days after their last treatment. A lot of those patients had gone approximately 45 days to 3 months. Does that answer your question?

DR. MARGOLIN: Actually, it is not responsive to the question but I think that is an important point because I think that is an extremely strict definition of non-resistant. It is very different, let's say, from greater than 12 months post-adjuvant therapy. But I will bet you the company has an idea about how many of the non-resistant patients still had room on anthracylcine as defined by less than a certain amount of prior -- would have had room if they were going into a study that had doxorubicin in it.

DR. RIVA: In fact, the majority of the patients non-anthracylcine-resistant received at least 5, 6 cycles of an anthracylcine-containing regimen as adjuvant. In Europe, normally we use 50 mg/m^2 or 60 mg/m^2, therefore, you can calculate around 300 mg/m^2, 350 mg/m^2, 360 mg/m^2. Therefore, it is clear that there is not a lot of room for these patients to receive another anthracylcine-containing regimen for at least 6 cycles. The maximum that you can deliver is 3 or 4 cycles.

DR. SCHILSKY: Just a couple of questions. In the TAX 303 study the sponsor presented a time to treatment failure analysis, which they said was a planned analysis in the protocol. You didn't present any such analysis. Did

you do such an analysis?

DR. GRIEBEL: I did not do such an analysis.

DR. SCHILSKY: Okay. I guess I would just like to get your opinion on the comparator toxicities. I am always a little bit concerned when we present the toxicity data for all grades of toxicity because I think it tends to magnify the appearance of the toxicity. Can you tell us what your assessment of the relative non-hematologic toxicity is if you focus on just grade 3 and 4 toxicity?

DR. GRIEBEL: I think if I was considering treating a patient with Taxotere and was counseling them on the side effects that we could potentially expect, things that I would mention, other than fluid retention syndrome obviously, would be diarrhea and the neurotoxicity.

MS. ZOOK-FISCHLER: I am going to play devil's advocate as a patient representative. It may not be exactly a question, but I am very concerned for the 44,000 women who are likely to die this year. With all this marvelous expertise, if a woman doesn't feel she is going to survive longer than a few months, I don't think it is going to be very significant. I think the endpoint, the bottom line for the patient is survival time. It seems to me, however you compare them, we are comparing one toxicity to another, and quality of life is compromised either way. I know from my own experience with women patients whom I counsel that a

woman who knows her survival is very limited, her quality of life is compromised regardless of which toxicity we are talking about. So, it is really a statement but I feel that needs to be addressed.

DR. SCHILSKY: Could I just follow-up on the question that Kim asked, because it seems to me that, in my mind, this is a fairly important issue. You kept highlighting for us, especially in the 304 study, that about 45% of the patients were not anthracylcine-resistant. So, could you tell me explicitly what message you are trying to send by highlighting that particular figure?

DR. GRIEBEL: That is basically focusing on what the labeled indication. The labeled indication seems to send the message of resistance of anthracylcine, and I was bringing out the fact that a fair percentage of these patients were not resistant and you could look at that both ways. You could look at it in terms of saying, well, if we approve this we could expand the labeled indication perhaps in consideration of that aspect.

DR. KROOK: I think I am following the same question a bit. In 303, I think you said that the there were 31% that were really receiving this as first-line metastatic disease therapy. If I look at what you have up there, it really is an equivalent study. Then I look at what the application goals are, and one says an expansion to

a label indication for treatment of patients with locally advanced who failed previous chemotherapy. So, my question is, does that include -- I mean, that includes adjuvant therapy, I believe. That is the indication that we are being asked about when we come to the questions also. But I have problems with that previous failed chemotherapy because there is almost 31% in the 303 who had not received previous therapy for metastatic disease, if I am right.

DR. GRIEBEL: And that was the reason to put that data point in.

DR. KROOK: So, almost a third is first-line therapy for metastatic disease.

DR. GRIEBEL: Right.

DR. KROOK: When you look at that 31% was there any difference? Obviously, there was probably a higher group of responders because they weren't heavily pretreated.

DR. GRIEBEL: I didn't look at that. Maybe the sponsor can address that question.

DR. DUTCHER: He is asking about the subgroup of the of the not resistant who had received their therapy for first-line treatment.

DR. RIVA: We had a look at this difference, and in fact there was a 49% of response rate in the Taxotere arm and 49% response rate in the doxorubicin arm in this sub-category of patients. So there was no difference in the

response rate. In this patient population subcategory the response rate is similar. We have the same data for time to progression, and the time to progression is also similar.

DR. LAMBORN: I am sorry, could you restate what you just said about time to progression? What is similar?

DR. RIVA: In the patient population who relapse more or equal to 12 months from the adjuvant, the time to progression also was similar between the two arms.

[Slide]

Here you have the results, median time to progression of 25 weeks versus median time to progression of 23 weeks in this subpopulation. Again, you see also that for the time to progression in all the most important prognostic factors of breast cancer. There is no difference, in fact, between the 2 arms.

DR. DUTCHER: When you say relapse less than 12 months, are those relapse of metastatic disease or are those relapse after adjuvant?

DR. RIVA: Relapse after adjuvant. So, they stopped the CMF and they relapsed after 12 months from the end of CMF. The other patients constituting the majority of the patient population received CMF for advanced disease, and among these patients we have resistant patients and not resistant patients.

DR. MARGOLIN: This might be better answered by

the sponsor unless you happen to know. If you could take us away from the tables and just tell us by gestalt or by your clinical impression, just how neurotoxic is Taxotere in terms of acute -- in terms of are myalgia symptoms similar to taxon or not? Whether steroids protect against that? And, finally, what you see in terms of cumulative toxicity and its reversibility? I am not asking for a comparison to taxon directly because that is not what we are here for, but really if we are going to move this drug into earlier treatment of patients with metastatic breast cancer and then eventually those patients will fail but they may live for a while longer, what shall we expect in terms of reversibility and chronicity in terms of neurotoxicity?

DR. CROWN: Well, obviously for the reasons you have outlined, it is a little bit difficult to get a handle on the long-term durations of neurological toxicity in a population of patients like this, but I would just emphasize that the percentage of patients who actually had the higher grades of neurological toxicity is very small. Patients often would be aware of some paresthesia, maybe some minor discomfort if you actually asked them about it, but in terms of actually causing a major inconvenience in their life or level of discomfort, that is not common. Certainly, it has been the experience of the taxanes in general, including Taxotere by the way, because we have patients on adjuvant

trials with Taxotere -- in my own institution we are studying Taxotere in the adjuvant setting, and we have quite a few patients now who have had a long time to recover and it does get better. It is slow, and it gets better over a number of months but there is an ongoing trend towards recovery.

DR. MARGOLIN: You don't see the acute arthralgia-myalgia syndrome?

DR. CROWN: Oh the acute syndrome is certainly seen from time to time. Again, I think the issue for dealing with the acute syndrome is just warning the patients in advance that it may happen and reassuring them, and when it doesn't come as a surprise to them it does not tend to be a very distressing side effect.

DR. TRUDEAU: I am Marie Trudeau, from Toronto. With respect to the two toxicities, neurotoxicity and myalgia in comparison to taxon, it is probably a little less than taxon. With respect to food retention, the fluid does dissipate, you know, several weeks or months following the discontinuation of the treatment.

DR. BURRIS: Burris, National. Not to belabor the point, I think that the comments that have been made by the two previous speakers were right on. In counseling a patient, in treating them off study, you would the tell them that by the end of 4 or 6 cycles of treatment you would

expect about 3%, 4%, or 5% of those patients to experience some numbness or tingling in their fingers and toes, which constituted the majority. During the early studies that Dr. Ravdin and I did in San Antonio and, in fact, having a neurologist evaluate those patients no neurotoxicity events could be documented by the neurologist.

In contrast with Dr. Crown's experience, I find -- maybe having treated many patients with a variety of analogs, the acute syndrome is really largely non-existent for arthralgias and neuralgias, and that is why it hasn't appeared, I think, on the majority of toxicity screens seen today.

DR. DUTCHER: Before you leave the microphone, could you just put it into perspective of someone who is trying to continue working and taking the drug? For example, a school teacher?

DR. BURRIS: Exactly, and I think that is a good point. By and large, I would say the majority of patients who are working are able to continue working while they receive their Taxotere treatment, putting that in the range probably upwards of 80% or 90%. I say that because the incidence of stomatitis is very minimal, but the neutropenia, documented again by some earlier studies that Dr. Ravdin and I performed where we did twice a week CBCs, in fact does occur on approximately day 7 and lasts for a

period of 24-72 hours. So, it is not long-lasting. In asking patients they will tell you they have a period of weakness and fatigue that occurs during those 2-3 days. There were several patients who were school teachers, patients whom I have treated in the past year, who were able to work throughout the school year, certainly in some adjuvant clinical trials that are ongoing where they received 6 cycles of the Taxotere-based regimen. I mean, the drug does have a significant myelosuppression pattern to it but it is very reversible, and has been shown to be non-cumulative.

As I commented earlier, I think that in quizzing patients in collecting data for studies, again, I think the fluid retention problem has moved largely to a case report phenomenon that isn't commonly complained about in patients not being treated on trial.

DR. TEMPLE: I have a semantic question. Usually, I guess, when we think of patients who have failed previous chemotherapy we are not thinking of the adjuvant setting. Maybe we could learn to but that isn't what we usually do. So, the data that would support the labeling modifications are a mixture of people who have failed adjuvant therapy and people who have failed some other therapy. Does this claim then become a sort of claim for first-line therapy in the usual terminology, and is that a problem? Would we usually

be asking for different kind of data?

DR. DUTCHER: I think that is a very good point. I think that that is why some of these questions have come up. Most of us think of failing prior therapy as failing prior therapy for advanced disease. So, you know, as you know, this is a rather fast-moving area of moving drugs up front, as we all saw two weeks ago. So, the question then becomes is this going to be approved for -- it would be approval for first-line therapy if it was approved for prior chemotherapy.

DR. TEMPLE: I guess depending on how you shape language.

DR. DUTCHER: Yes.

DR. TEMPLE: If it were for first-line, would doxorubicin alone be the right comparator, or have events passed that by for the initial therapy? Would it usually be a combination?

DR. DUTCHER: It would be a combination.

DR. LAMBORN: Do we have the option of redefining? I assume we do. So, we could choose to define failed therapy more narrowly if we choose to.

DR. DUTCHER: Correct. Yes?

DR. RAVDIN: Peter Ravdin, San Antonio. I would just like to say that as a practical matter these days, essentially all the protocols in the United States use

anthracyclines and deliver a dose of anthracyclines that makes continuing therapy with anthracyclines impractical. So, for many of these patients, they have essentially failed what most people consider as the best front-line therapy whether or not it is delivered as an adjuvant therapy or as the first therapy for metastatic disease, and that is therapy that is based on anthracyclines.

DR. TEMPLE: Yes, but this was a trial in people who hadn't had anthracyclines. Right? They had something else, either adjuvant or as treatment but not anthracyclines. That is why you could compare it with doxorubicin.

DR. DUTCHER: Correct. Dr. Schilsky?

DR. SCHILSKY: Just to clarify Dr. Temple's point, I mean, as I read the current indication it would permit for use of Taxotere as front-line therapy for metastatic disease in patients who have relapsed during anthracylcine-based adjuvant therapy. So, that is the current indication. So, I don't know that the proposed indication moves us into the realm of a different group of patients than the current indication already permits.

DR. DUTCHER: I think the point is well taken that anthracyclines are currently standard adjuvant treatment. Any further comments for discussion?

Committee Discussion and Vote

DR. DUTCHER: I guess we will address the questions. We will take a moment to look at the first page. Proposed Indication: The study is proposed to support conversion of Taxotere's accelerated approval to full approval for the current labeled indication "for treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracylcine-based therapy or have relapsed during anthracylcine-based adjuvant therapy". Then it presents the studies that have been completed and the studies that are ongoing.

Question number one, is TAX 304 an adequate and well-controlled trial that provides substantial evidence of Taxotere's efficacy and safety in the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracylcine-based therapy or have relapsed during anthracylcine-based adjuvant therapy? Dr. Margolin?

DR. MARGOLIN: I vote yes.

DR. DUTCHER: Dr. Schilsky, any comment?

DR. SCHILSKY: No, I would agree. I believe the answer should be yes.

DR. DUTCHER: All those who would vote yes to question number one?

[Show of hands]

Eight. Unanimous, eight yes.

Number two, is it the recommendation of the Committee to convert Taxotere from accelerated approval to full approval for the currently labeled indication, provided that the applicant agrees to complete studies TAX 311 and TAX 313 as Phase IV commitments? Dr. Margolin?

DR. MARGOLIN: Yes.

DR. DUTCHER: All those who would vote yes, please raise your hand.

[Show of hands]

Eight yes.

Moving on to TAX 303, the applicant proposes to use TAX 303 as an expansion of the labeled indication from "for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracylcine-based therapy or have relapsed during anthracylcine-based adjuvant therapy" to "for treatment of patients with locally advanced or metastatic breast cancer who have failed previous chemotherapy."

The first question, noting that the sole evidence of superior efficacy for docetaxel over doxorubicin was a statistically higher overall response rate, does the Committee agree that TAX 303 provides substantial efficacy and safety data to support expansion of the labeled indication to "the treatment of patients with locally advanced or metastatic breast cancer after failure of

previous chemotherapy?" Dr. Lamborn?

DR. LAMBORN: Perhaps this is a situation where we should divide it into two parts. One is that they have previously failed just adjuvant therapy versus whether or not they have failed therapy for metastatic disease. That is the piece that I was hearing earlier, that you would not want to recommend this in first-line therapy for patients who had not had the prior course --

DR. DUTCHER: But they are getting anthracylcine now as adjuvant in the United States. So, they will have had the anthracylcine. I mean, that would fit the current indication.

DR. LAMBORN: You are saying that they do, but that is an issue of practice, not an issue of a statement of indication.

DR. SCHILSKY: I am not entirely happy with this wording. There might be other wording that could be suggested, but in my mind the issue is that it is commonplace to use anthracylcine-based adjuvant chemotherapy these days for most women by the time they complete 6 cycles of an anthracylcine-based regimen, and they will have gotten about 360 mg/m^2 cumulative dose of Adriamycin. It is somewhat striking to me that in the studies that we have heard today most of the cases of significant cardiac toxicity actually occurred at cumulative doses less than 46

mg/m^2. So, there is not a window of great opportunity for additional Adriamycin chemotherapy for those women who relapse at some point in the future after having received a cumulative dose of 360 mg/m^2. It would certainly seem to me that those women are likely to benefit from therapy with Taxotere, and it would probably have a more favorable toxicity profile in that group of patients than by giving them additional doxorubicin at that point.

So, it seems to me that we should consider whether it is possible to frame the language of the indication to include those women for whom additional anthracylcine therapy may be contraindicated.

DR. DUTCHER: So, you would prefer to keep it as for those with prior anthracylcine or those for whom anthracylcine is not indicated?

DR. SCHILSKY: Well, my personal preference, I think, would be to modify the current indication by adding an additional phrase to say that it would be indicated as currently stated and for those women in whom anthracylcine chemotherapy is contraindicated.

DR. TEMPLE: Well, they already have a complete claim which we would modify to be even more complete for people who have been exposed to an anthracylcine. That is what the previous discussion just handled. Not only do they not have to progress on it, but if they just even looked at

it then they can -- okay? That is what 304 takes care of. This is about people who haven't had any doxorubicin, any anthracylcine, and that is the question.

DR. SCHILSKY: That is not actually how I understood the prior study, which does not include the population of patients who may have received a full course of anthracylcine therapy as adjuvant treatment and at some point greater than 12 months later have relapsed. Those patients are not included in either of the studies that were presented today.

DR. DUTCHER: The indication says "progressed during" so that means on study.

DR. TEMPLE: The current indication.

DR. DUTCHER: Or "relapsed during."

DR. SCHILSKY: Right.

DR. DUTCHER: So, it suggests they are getting that treatment now, not 6 months later.

DR. SCHILSKY: So, the current indication, as I understand it, does not include the clinical circumstance I just described where a woman might have received a course of anthracylcine-based adjuvant therapy and at some future time will have relapsed.

DR. TEMPLE: But the change you just agreed to --

DR. SCHILSKY: The change that was proposed.

DR. DUTCHER: We didn't agree to approve that yet.

DR. TEMPLE: Sorry, let me come back. One possible change is to make it clear that you don't have to have actually progressed on anthracylcine and failed. Another possible change, which is the one that is the immediate subject of this question, is to divorce the whole question from having any exposure to anthracylcine, and that is what study 303 arguably is about. None of those people had any anthracylcine.

DR. SCHILSKY: Right. Well, I guess that is why I am a little bit uncomfortable with perhaps broadening it to that extent because it is not clear to me that 303 demonstrates that Taxotere is superior by any measure to doxorubicin. It does clearly have a different toxicity profile. I think it is clear that there are patients for whom the physician is likely to feel that doxorubicin is not an appropriate therapy, perhaps because of risk of cardiac toxicity, and I think that in those circumstances Taxotere would be an appropriate therapy.

DR. TEMPLE: So, you are saying that there still is an order to this, that the first thing you should think of in people who fail their alkylating agent, or whatever it is, is doxorubicin, and not Taxotere.

DR. SCHILSKY: I say that based upon the results of the 303 study which was powered to demonstrate superiority to doxorubicin and failed to do so.

DR. TEMPLE: Well, it wasn't superior but does it have to be superior?

DR. SCHILSKY: Well, I think it is clear that it is not superior. It is also not clear that it is equivalent.

DR. TEMPLE: Well, that is all worth discussing. I guess the question is if you thought that study made a persuasive case for equivalence, would you then still think it should only be for people who can't get doxorubicin?

DR. SCHILSKY: I guess I would answer that by saying yes if I thought that the study made a persuasive case for equivalence but I don't think it does.

DR. TEMPLE: Okay. I have to throw one other thing in. This is a study in which the effectiveness of the new treatment, Taxotere, is being entirely based on evidence that it is equivalent to a drug we know works. So, if you don't think it makes the case for equivalence, then you also don't think it shows effectiveness.

DR. SCHILSKY: Oh, no, no. Don't put those words in my mouth.

[Laughter]

DR. TEMPLE: I don't understand how you could possibly --

DR. SCHILSKY: Well, I think the drug is clearly active -- I think the drug is clearly active in the disease,

as demonstrated by a statistically superior response rate. So, then it gets into the issue of the clinical benefit issue. But I think, you know, in my mind the data do not demonstrate superiority to doxorubicin. The data, I think, do not persuade me that the two are equivalent, but I am persuaded by the 303 data and the sort of universe of data with Taxotere in breast cancer that the drug has a high level of activity in breast cancer, and has a toxicity profile which may be more appropriate for certain groups of patients than doxorubicin.

DR. TEMPLE: Let me just press this point. Except in the refractory setting where we have an explicit policy, supported on many occasions by the Committee, by relying on a surrogate endpoint, namely, evidence of activity, for approval, this Committee and the Agency has generally felt that for other stages of breast cancer you need evidence of clinical benefit, not just evidence of activity.

So, you know, we need to know if you are recommending a change in that standard or, as an alternative, do you actually think there is some evidence that there is some clinical benefit based on the discussion that was held earlier on equivalence or non-inferiority.

DR. MARGOLIN: Just a couple of thoughts, and not very formal and not going to sound very elegant, but I mean, we agree that by strict statistical standards this is not

powered to be an equivalence study, but I think we also agreed earlier that it was safe to say that Taxotere is not inferior by more than 1.16 hazard ratio, if I got that right. So, you could certainly say it is not inferior by some reasonable margin. Then you have activity using response rate as our surrogate, which is rather impressive.

I don't think that these indications where you rigidly allow only patients who have failed or can't be treated with, or this or that, are very useful. So, I think what we really have to decide is whether we feel comfortable that we are not endangering patients by approving this for what would turn out to be first-line therapy for those patients who only have had, say, CMF regimen therapy and then relapse, and then the doctor has to choose whether to put them on doxorubicin or on Taxotere. If we approve this drug, have we done a disservice by saying that it is okay to give those patients first-line therapy with Taxotere for their metastatic disease?

DR. DUTCHER: I don't think that right now we can tell you that there has to be a strict order between the anthracyclines and the taxanes, I mean, you know, not just the data here but the global experience. I mean, I think exactly what Kim said is correct. If there is a difference, it is small enough that nobody is going to feel bad about

going one way or the other, T first and then A, or A first and then T.

DR. TEMPLE: But you would also think that in a person who had failed CMF adjuvant therapy it would be perfectly reasonable to use either doxorubicin or Taxotere as the complete first-line therapy. That is okay? I am not offering an opinion; I am just asking. I have no idea whether that makes sense but I want to know what you think.

DR. DUTCHER: What I think? What I think is that it probably makes no difference, but I am not in charge of a breast cancer in a cooperative group.

[Laughter]

DR. BURRIS: I realize it is not my place to speak and I want to turn it over to Peter Ravdin who is a SWOG executive officer, but I think you are talking about the same thing, and that is what I took away as the point of the trial and the next trials that we are forming, that this offers an option to a patient who has had prior chemotherapy and in what direction the physician would head. I think that is supported by the data from study 1193. Peter?

DR. RAVDIN: Actually, what that study showed, and just to remind you, it is a 3-arm study, it showed that between anthracylcine and taxol there was no difference in response rate. The combined therapy was a little bit better but there was no difference in overall survival.

I think I have heard that study presented in various ways, but one of the ways it has been presented is that perhaps in selected patient population either of the first agents as single agents would be perfectly reasonable therapy.

DR. DUTCHER: Thank you. Other comments?

DR. GRADISHER: Gradisher, from Chicago. There is one other corollary to what Peter was talking about in the same study. There was a crossover design built into it. So that gets to the question of sequence and priority of which drug comes first. It didn't make a difference.

DR. DUTCHER: Are you all prepared to vote?

DR. MARGOLIN: I just have one question, would Dr. Temple want us to change and add to the first half of the first sentence a statistically higher overall response rate and a not statistically inferior time to progression, or something like that?

DR. TEMPLE: No, you don't have to do that but at some point we need to know why -- and, you know, we will go back and my expectation is that the company will want to address this matter a little more -- just why they think this study didn't show a difference between treatments. This is a standard non-inferiority problem. It is getting a lot of discussion in a lot of places and it doesn't seem fully addressed yet. But we would understand you to be

saying that the study -- it isn't clear Dr. Schilsky believes this, but some of you may believe it, that the study is a persuasive case for non-inferiority by more than a little bit, and that that is pretty good evidence of effectiveness. That is what you would say if you thought this was reasonable, and that is how we would understand your favorable vote.

DR. LAMBORN: I think it is important that it is clear that it is not because of the superior response rate that we would be saying yes to this, but because of the demonstration that the time to progression and survival is not majorly inferior, and it would be nice if ultimately we had some more specifics that would further describe that. But I think the data is the there.

DR. DUTCHER: Dr. Crown?

DR. CROWN: There is one other point which hasn't come up much in the discussion which we presented, this is the fact that there was a difference in time to failure. The time to failure took into account other causes of failure, other than progression of disease and, of course, in the situation that we had in the study there were more patients who had to stop treatment on the doxorubicin arm because of toxicity or withdrawal of consent than was the case on the Taxotere arm. I think that has some relevance.

In addition to that, there is another potential

issue here. To be very fair to doxorubicin, in the study we did not go beyond 7 cycles except in a very small number of patients. Of course, in practice with Taxotere the treatment often continues for patients with an ongoing response for a number of cycles longer than that, and it is entirely possible that a little more of a push in that direction might have had an impact in what was a difference, albeit not a statistically significant one in terms of TTP, unlike TTF.

DR. TEMPLE: We have had to grapple with this question too. Time to treatment failure is not a pure effectiveness measurement, as you all know. It is a complicated measure and it may have a lot to do with which drug to choose, but it doesn't have anything to do -- it doesn't have much to do or it is not solely related to whether a drug works. So, we tend to not pay much attention to it as an efficacy measure.

DR. DUTCHER: One more comment.

DR. DURRLEMAN: Just to follow-up on Dr. Temple's question earlier, I did some, you know, back of the envelope calculations. I think what we can confidently say is that the median time to progression with Taxotere would not be a failure -- from the median time to progression on doxorubicin -- by more than about 2-3 weeks, with the confidence interval and the hazard ratio that we have.

Again, this is the boundary for non-inferiority that we have.

DR. DUTCHER: Any other discussion? I didn't mean to make it sound like we couldn't have any more comments. Any more comments?

[No response]

So, question number one, does the Committee agree that TAX 303 provides substantial efficacy and safety data to support expansion of the labeled indication to "the treatment of patients with locally advanced or metastatic breast cancer after failure on previous chemotherapy?" Dr. Schilsky?

DR. SCHILSKY: I would stick by my guns and say no.

DR. MARGOLIN: I will stick by my guns and say yes.

[Laughter]

DR. DUTCHER: All those who would vote yes, please raise your hand.

[Show of hands]

Seven yes, and one no. We appreciate those who stick by their guns.

If expansion of the currently labeled indication for Taxotere -- well, we don't have to answer number two. Okay. Any other clarifications the Agency needs? No?

Done?

All right, thank you very much. Just to remind those of you who are coming back tomorrow, we are starting at 8:00 a.m., not 8:30.

[Whereupon, at 5:05 p.m., the proceedings were recessed to be resumed at 8:00 a.m., Tuesday, June 2, 1998.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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