AT DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

DAY TWO

Thursday, September 7, 2006

8:00 a.m.

Hilton Silver Spring
Silver Spring, Maryland

PARTICIPANTS

Maha H.A. Hussein, M.D., FACP, Acting Chair
Johanna M. Clifford, M.Sc., RN, Executive Secretary

MEMBERS:

Ronald M. Bukowski, M.D.
David Harrington, Ph.D.
Alexandra M. Levine, M.D.
Michael C. Perry, M.D.
Maria Rodriguez, M.D.

CONSUMER REPRESENTATIVE:

Pamela J. Haylock, RN

NON-VOTING INDUSTRY REPRESENTATIVE:

Antonio J. Grillo-Lopez, M.D.

CONSULTANTS (VOTING) FOR ABRAXANE:

John Carpenter, M.D.
Nancy Davidson, M.D.
Michael Link, M.D.
Gary Lyman, M.D.
Richard Simon, D.Sc.
Sandra Swain, M.D.
Jurgen Venitz, Ph.D.

PATIENT REPRESENTATIVE (VOTING):

Natalie Compagni Portis (By telephone)

FDA STAFF:

Richard Pazdur, M.D.
Robert Justice, M.D.
John Johnson, M.D.
Patricia Cortazar, M.D.
Rajeshwari Sridhara, Ph.D.
Brian Booth, Ph.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order

DR. HUSSAIN: If you can all have your seats, we are going to start this morning's session of ODAC, dealing NDA 21-660 Abraxane.

Before we begin, please make sure that you switch your cell phones and your pagers.

My name is Maha Hussain. I would like to begin, first of all, welcoming you all, and with the introduction of the Committee. We will begin with Dr. Pazdur.

Introduction of Committee

DR. PAZDUR: Richard Pazdur, Office Director, FDA.

DR. JUSTICE: Robert Justice, Division Director, FDA.

DR. JOHNSON: John Johnson, Clinical Team Leader, FDA.

DR. CORTAZAR: Patricia Cortazar, Medical Reviewer, FDA.

DR. SRIDHARA: Rajeshwari Sridhara, Statistical Team Leader, FDA.

DR. BOOTH: Brian Booth, Clinical Pharmacology, FDA.

DR. DAVIDSON: Nancy Davidson, Medical Oncologist, Johns Hopkins.

DR. CARPENTER: John Carpenter, Medical Oncologist, University of Alabama at Birmingham.

MS. HAYLOCK: Pamela Haylock, Oncology Nurse and Consumer Representative, UTMB, Texas.

DR. LYMAN: Gary Lyman, Consultant and Medical Oncologist, University of Rochester.

DR. HUSSAIN: Ms. Portis, are you on the phone with us?

MS. PORTIS: Yes, I am.

DR. HUSSAIN: Would you please introduce yourself?

MS. PORTIS: Yes. This is Natalie Compagni Portis, Patient Representative.

DR. HUSSAIN: Thank you.

Maha Hussain, University of Michigan, Medical Oncology.

MS. CLIFFORD: Johanna Clifford, Executive Secretary to the ODAC, FDA.

DR. PERRY: Michael Perry, Medical Oncologist, University of Missouri, Ellis Fischel Cancer Center.

DR. HARRINGTON: David Harrington, Statistician, Dana-Farber Cancer Institute.

DR. LINK: Michael Link, Pediatric Oncologist, Stanford.

DR. RODRIGUEZ: Maria Rodriguez, Medical Oncologist/Hematologist, M.D. Anderson Cancer Center in Houston, Texas.

DR. BUKOWSKI: Ron Bukowski, Medical Oncologist, Cleveland Clinic.

DR. LEVINE: Alexandra Levine, Hematology/Oncology, USC/Norris Cancer Hospital.

DR. VENITZ: Jurgen Venitz, Pharmacologist, Virginia Commonwealth University.

DR. SIMON: Richard Simon, Chief of the Biometric Research Branch, National Cancer Institute.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez, Hematologist/Oncologist, and the Industry Representative on this committee. I do not receive

any compensation whatsoever from industry for my participation at these meetings.

DR. HUSSAIN: Thank you. We will wait for Dr. Swain.

DR. SWAIN: Dr. Sandra Swain, National Cancer Institute.

DR. HUSSAIN: Thank you.

The Conflict of Interest Statement will be presented by Johanna Clifford.

Conflict of Interest Statement

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

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. Section

208(b)(3), full waivers have been granted to the following participants:

Dr. Ronald Bukowski for unrelated consulting for a competitor for which he receives less than 5,001 per year, also, for his unrelated speakers bureau activities for a competitor. He receives less than 5,001 per year.

Dr. John Carpenter for his unrelated speakers bureau activities for a competitor for which he receives less than 10,001 per year.

Dr. David Harrington for his employer's research contract with a competitor for which his employer receives less than 100,000 per year.

Dr. Alexandra Levine for her unrelated speakers bureau activities for a competitor for which she receives less than 10,001 per year.

Dr. Maha Hussain has been granted full waivers under 18 U.S.C., Section 208(b)(3) and 21 U.S.C. 355(n)(4), for her and her spouse's stock ownership in three competing firms. One is valued at less than 5,001, and two are valued between 5,001 and 25,000 per firm.

In addition, in accordance with 21 U.S.C. 355(n)(4), waivers have been granted to the following participants:

Ms. Pamela Haylock for her and her spouse's stock ownership in two competing firms. One is worth less than 5,001, and the other is worth between 5,001 and 25,000. Because these stock interests fall below the de minimis exception allowed under 5 CFR 2640.202(b)(2), a waiver under 18 U.S.C. 208 is not required.

Dr. Michael Perry for his ownership in stock of two competing firms. One is worth less than 5,001, the other is worth between 5,001 and 25,000. Because these stock interests fall below the de minimis exception allowed under 5 CFR 2640.202(b)(2), a waiver under 18 U.S.C. 208 is not required.

Waiver documents are available at FDA's Dockets web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table.

In addition, copies of all the waivers can

be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Antonio Grillo-Lopez has been invited to participate as a non-voting industry representative acting on behalf of regulated industry. Dr. Grillo-Lopez is a retired employee of Neoplastic and Autoimmune Diseases Research Institute.

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

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

Thank you.

DR. HUSSAIN: Thank you, Johanna.

I would like to invite Dr. Pazdur, the Director of the Office of Oncology Drug Products for opening remarks.

Opening Remarks

DR. PAZDUR: Good morning. Adjuvant breast cancer indications have been supported by large randomized clinical trials examining the efficacy and safety of new agents compared to standard therapies.

These trials have usually enrolled several thousands of patients. The adjuvant indication is a unique indication. It has a different risk-benefit consideration from the metastatic disease indications. Adjuvant therapies are designed to offer a curative potential to patients at risk for disease recurrence.

In essence, from a public health standpoint, the adjuvant indication is a high bar indication, high bar in terms of efficacy, high bar in terms of the demonstration of a safety profile.

Our progress in the adjuvant therapy of

breast cancer has been measured by progressive incremental survival gains with successive trials being built on past advances. The acceptable safety profile of agents introduced in the adjuvant setting may be different from those considered in the metastatic disease setting.

Chronic toxicity, such as neurotoxicity and other end organ damage, must be carefully documented and minimized since these toxicities may affect patients for years after the adjuvant therapy has been completed.

The Agency's viewpoint has been that our gains in adjuvant therapy of breast cancer should be carefully guarded and any even potential decrements in efficacy must be carefully characterized and adequately justified in a risk-benefit analysis.

Abraxane is an albumin-bound form of paclitaxel. Abraxane was approved by the FDA in January 2005 for a previously approved Taxol metastatic disease indication. Because Abraxane and Taxol are both paclitaxel formulations, this

metastatic disease approval was based in part on the 505(b)(2) section of the Federal Food, Drug and Cosmetic Act.

This provision allows the FDA, where appropriate, to provide new formulations of marketed drugs entirely or partially on studies not conducted by the applicant and for which the applicant has not obtained a right of use.

The provision allowed Taxol's preclinical genetic toxicology studies to support Abraxane's indication. A randomized clinical trial comparing Abraxane to Taxol led to the approval of this metastatic indication. Response rate rather than a time to progression endpoint, such as survival or TTP, was used as the basis of approval.

We are holding this ODAC meeting to discuss a drug development proposal for Abraxane in the adjuvant therapy of breast cancer. The sponsor has met with the agency on several occasions and requests a different pathway for approval of this adjuvant indication. This proposal does not include a large randomized study to characterize

the relative efficacy and safety of the new agent to a standard therapy.

Instead, their request again relies in part on the 505(b)(2) regulatory provision. The sponsor's plan relies on the results of the randomized Intergroup study that was the basis for the Taxol adjuvant treatment of node-positive early breast cancer, Taxol's preclinical toxicology studies, the results of the trial supporting the 2005 approval of Abraxane in the metastatic disease setting, and a 30-patient, single arm safety study in the adjuvant setting.

Initially, a proposed 400 randomized patient study was proposed comparing Abraxane to Taxol in the adjuvant treatment of node-positive early breast cancer was proposed, however, this proposal has been changed to be conducted after the approval of this indication and is now of unprespecified size or unspecified size.

Abraxane and Taxol are not bioequivalent, hence, Abraxane cannot be considered a generic equivalent of Taxol. There are distinct differences

between Taxol and Abraxane that should be considered throughout the discussions of this drug development proposal.

Pharmakinetics of total paclitaxel are different between the two drugs. Although the measurement of free paclitaxel may provide a more accurate depiction of the relative pharmakinetics of the two drugs, information on the comparative pharmakinetics of free paclitaxel generated from these two drugs is currently unknown.

Also, comparisons of the biodistribution of the drugs are not known. The two drugs have different formulations and different infusion rates. The two drugs have different toxicity profiles. The two drugs have different response rates in the metastatic disease settings.

In contrast to the sponsor's proposal, the agency has encouraged the sponsor to conduct randomized studies that could be either of a conventional superiority trial or a non-inferiority trial.

Superiority trials are generally preferred

and usually require smaller sample sizes than non-inferiority trials and provide direct measurements of efficacy.

Non-inferiority trials are indirect measures of efficacy and must preserve a percent of a known treatment effect of a standard drug. The lower the percent retention of the treatment effect in a non-inferiority trial results in a smaller trial size, however, it also increases the potential loss of efficacy.

In listening to the presentations and the proposal for the adjuvant indication by the sponsor, I encourage members of the committee to deliberate on the risk-benefit of the approval of Abraxane in the adjuvant setting without a conventional large randomized trial documenting efficacy and safety in the population.

Simply that a drug has greater perceived efficacy in the metastatic disease setting does not obviate the need for a conventional adjuvant study. All drugs that have been introduced into adjuvant trials in breast cancer, and these trials have

enrolled thousands of patients, have demonstrated enhanced activity in the metastatic disease setting.

Large randomized trials provide important information to patients in making decisions regarding which drug they should take.

Without the information that can be derived from a large randomized trial, the essential question that the committee must keep in mind in their deliberations is one of risk-benefit to the American public, what is the potential benefit of Abraxane to outweigh a potential loss of efficacy in a potentially curative disease setting.

Thank you.

DR. HUSSAIN: Thank you, Dr. Pazdur.

We will begin with two sets of presentations. The first will be by the sponsor, and the second will be by the FDA.

I would like to invite Dr. Michael Hawkins to present.

Abraxis Bioscience, Inc.

Sponsor Presentation

Abraxane: Background and PK/Safety Comparisons with Taxol

DR. HAWKINS: Thank you, Dr. Hussain, and thank you, Dr. Pazdur. I would also like to thank the FDA and the Advisory Committee members for giving us this chance to discuss the approval criteria for Abraxane as adjuvant treatment of node-positive breast cancer.

I am Dr. Mike Hawkins. I am the Chief Medical Officer of Abraxis Bioscience.

[Slide.]

The purpose of this meeting from our perspective is to determine if, under the 505(b)(2) pathway, an efficacy trial in the adjuvant treatment of node-positive breast cancer is required to approve Abraxane in this setting.

To under Abraxis' position on this matter, I first have to review briefly the 505(b)(2) mechanism that Dr. Pazdur just alluded to.

[Slide.]

The 505(b)(1) is the typical way most drugs are approved, and they are the types of

applications this committee is most used to seeing.

505(j) is used for the generic approvals, which does not apply to Abraxane, as Dr. Pazdur pointed out.

The 505(b)(2) allows the sponsor to rely on investigations to which it does not have the right of reference, specifically, data in the literature and data in approved NDAs for the reference listed drug. In this case, the reference listed drug is Taxol.

[Slide.]

Dr. Woodcock summarized the FDA's position regarding 505(b)(2) in 2003, said the agency's approach is to use the 505(b)(2) drug approval pathway to avoid studies that are not scientifically necessary.

The conduct of duplicative studies would slow the process of drug approval with no corresponding benefit to the public health.

[Slide.]

This pathway has been used extensively by the FDA to approve more than 80 different drugs in

a wide range of applications.

[Slide.]

The other factor that has gone into Abraxis' position on this issue is a unique set of circumstances that relate to Abraxane. As Dr. Pazdur mentioned, the active ingredient of Abraxane and Taxol is identical, i.e., paclitaxel. Paclitaxel is already approved as adjuvant therapy in breast cancer at a Taxol dose of 175 mg/m2.

By removing Cremophor from the formulation, Abraxane is able to deliver a higher dose of paclitaxel, namely, 260 mg/m2.

At these doses, superior antitumor activity for Abraxane over Taxol was demonstrated in metastatic breast cancer, however, the tolerability of the higher Abraxane dose was comparable to that of the lower Taxol dose due to the removal of Cremophor from the formulation.

As Dr. Pazdur pointed out, Abraxane was approved in metastatic breast cancer under the 505(b)(2) regulatory statute.

The approach that Abraxis would like to

take at this point is to extend the 505(b)(2) mechanism to the approval of Abraxane in the adjuvant setting.

[Slide.]

Our position is that we believe that an efficacy trial in the adjuvant treatment of breast cancer is not scientifically necessary and would significantly delay the approval of a Cremophor-free paclitaxel alternative for physicians and the patients.

To clarify, though, Abraxis is committed to conducting a comparative safety trial of Abraxane versus Taxol for women with node-positive breast cancer. Judging from the question to the committee, I think there has been some confusion about Abraxis' position with respect to this.

We have always been committed to conducting a safety study. Our issue was with having to conduct a very, very large-scale trial for efficacy endpoints.

[Slide.]

Our presentation will focus on the reasons

that an efficacy adjuvant trial should not be required for the approval of Abraxane.

Abraxane, as I have already noted, is a Cremophor-free formulation of paclitaxel. By removing Cremophor, Abraxane allows safe delivery of higher doses of paclitaxel, and I will show you data on that.

In metastatic breast cancer Abraxane has demonstrated greater antitumor activity than Taxol.

As we have noted, paclitaxel is currently approved for use using the data from the Taxol NDA.

The Abraxane dose of paclitaxel is safe and higher than the already proven effective dose in the adjuvant setting.

For these reasons, we feel that there is no scientific basis to hypothesize that Abraxane will be less effective than Taxol as adjuvant therapy in breast cancer.

[Slide.]

As part of our presentation, I will describe the two formulations of Taxol and Abraxane, and then I will review the safety data

regarding the higher dose of Abraxane.

Dr. Gradishar will then discuss the antitumor activity, the comparative antitumor activity of Abraxane in Taxol, and then finally, Dr. Hudis will provide his perspectives on the use of Abraxane in the adjuvant setting.

[Slide.]

To start with, just let me give you a brief historical background. As you know, paclitaxel is one of the most active cytotoxic agents available. Cremophor, though, is required in high concentrations in this formulation due to the water insolubility of the drug.

In the 1990s, Abraxis developed a paclitaxel formulation that replaced Cremophor with albumin, and this is the Abraxane formulation.

Preclinical studies subsequently demonstrated that Abraxane significantly and consistently improved the therapeutic index of paclitaxel.

[Slide.]

In 2001, after we completed Phase 1

studies and Phase 2 trials in metastatic breast cancer, the FDA agreed that Abraxane could receive approval in the metastatic setting with the same indication as Taxol under the 505(b)(2) regulatory pathway provided that there were two issues satisfied:

First, that the replacement of Cremophor with albumin did not result in a decrease in the efficacy of paclitaxel; and secondly, that the higher dose of 260 mg of Abraxane could be administered with comparable tolerability to that of the lower dose, 175 mg of taxol.

In 2004, the results of the randomized Phase 3 head-to-head comparison of Abraxane versus Taxol were known. That trial demonstrated that not only was the antitumor activity preserved, but that Abraxane actually demonstrated superior antitumor activity to Taxol. As Dr. Pazdur mentioned, the primary endpoint of that study, and the endpoint agreed to for approval, was response rate.

In addition, while the toxicity profiles are different, the overall tolerability of the two

drugs was the same.

On that basis, in January of 2005, Abraxis was granted approval of Abraxane for treatment in metastatic breast cancer under the 505(b)(2) regulatory pathway for new formulations of existing drugs.

[Slide.]

I would now like to turn to the differences in the two formulations.

[Slide.]

In Abraxane, paclitaxel is complexed in albumin particles, which are stable and keep paclitaxel in an amorphous, non-crystalline state. When diluted to concentrations that are typically seen in the plasma of patients receiving Abraxane, the albumin particle dissociates into the individual albumin molecules. At this point, the paclitaxel is circulating as albumin or protein-bound drug.

[Slide.]

This is a description of the precise formulations of the two drugs. For each milligram

of paclitaxel in the Abraxane formulation, there are 9 milligrams of albumin. There are no solvents whatsoever in the Abraxane formulation, therefore, it is a Cremophor-free formulation of paclitaxel.

Taxol, however, is supplied with Cremophor approximately 100 milligrams for every milligram of paclitaxel and approximately 70 milligrams of ethanol for every milligram of paclitaxel.

[Slide.]

The presence of Cremophor in the Taxol formulation has resulted in this black box warning for hypersensitivity reactions which are related to the presence of Cremophor in the Taxol formulation.

These hypersensitivity reactions and anaphylaxis can occur in 2 to 4 percent of patients receiving Taxol in the clinical trials, and fatal reactions have occurred despite adequate premedication prior to dosing.

The premedication includes premedication with dexamethasone, and even as a premedication, the dexamethasone can cause problems. Hyperglycemia can occur at times and glucose

intolerance in diabetics has certainly been reported. Also, very disturbing to patients are mood changes and insomnia which occur following the dexamethasone.

[Slide.]

In contrast, Abraxane's package insert specifically indicates that no premedication to prevent hypersensitivity reactions is required prior to administration of Abraxane.

[Slide.]

I would now like to turn to the differences in the pharmacokinetics that Dr. Pazdur just alluded to.

We believe that these differences in the pharmacokinetics are completely explainable by removing Cremophor from the formulation, and therefore are an understandable and actually essential part of developing a Cremophor-free formulation of paclitaxel.

These differences relate to the linearity of the pharmacokinetics and alterations in the distribution phase of paclitaxel when given as the

two drugs.

[Slide.]

Cremophor forms micelles in the plasma and entraps paclitaxel. This results in non-linear paclitaxel pharmacokinetics when paclitaxel is administered as Taxol.

[Slide.]

On the left-hand side of this curve shows the non-linearity of the paclitaxel when given as Taxol. In contrast, when paclitaxel is given as Abraxane, the pharmacokinetics are linear and predictable, reflecting the absence of Cremophor in the formulation.

[Slide.]

The other effect that Cremophor has on the pharmacokinetics relates to the distribution phase of the drug. These are data from a clinical trial that we conducted comparing Abraxane and Taxol at the doses and schedules that were used in the Phase 3 trial and which are proposed for use in the adjuvant setting.

The Abraxane dose was approximately 50

percent higher than the Taxol dose reflecting the removal of Cremophor from the formation, and because the risk of hypersensitivity reactions was greatly reduced by removing Cremophor, the drug could be given over one sixth the time, 30 minutes versus 3 hours.

A total of 26 patients were randomized to the two treatment arms, and the first thing that you notice from these two curves is the very high peak concentrations that were achieved with Abraxane. These peak concentrations are related to two factors. One is the dose, which is 50 percent higher for Abraxane, and the second is the 30-minute infusion for Abraxane compared to Taxol.

When you correct the Cmax for dose, as shown in this graphic, the difference between the Cmax is still 4.5 fold, and this is explained by 1/6th the shortening of the infusion rate for Abraxane.

The other difference in the pharmacokinetics relates to the area under the curve. The area under the curve when corrected for

dose is 25 percent higher for Taxol than it is for Abraxane, 71.9 versus 56.8.

This difference occurs in the distribution phase of the two drugs, and again is related to the Cremophor sequestration of paclitaxel in the plasma during this period.

When you look at the volume of distribution in the clearance, which are calculations that are derived from the area under the curve, the differences in those PK parameters occurred because of this difference in the areas under the curve.

When you look at the terminal phase or the elimination phase of the drug, which is dominated by metabolism and excretion, the half-lives for Taxol and Abraxane are identical, 21.6 hours for Abraxane, 20.5 hours for Taxol.

[Slide.]

I would now like to turn to the data that demonstrate that removing Cremophor allows the delivery of higher doses of paclitaxel, and that this increased paclitaxel delivery can be done

safely.

[Slide.]

We have data from two sources to address this issue. The first is our randomized trial which Dr. Pazdur has already alluded to in metastatic disease. This trial compared Abraxane at 260 mg to Taxol at 175 mg, and I will show you the data from that study.

Secondly, we do have a pilot experience using Abraxane in the adjuvant setting at a dose again of 260 mg, this time administered in a dose-dense fashion every two weeks. I am going to go over the data from these two trials.

[Slide.]

First, let's turn to the metastatic setting. This trial was known to us as CA012. It was a randomized Phase 3 trial of Abraxane versus Taxol in metastatic breast cancer.

The doses are shown on this slide. The planned dose for Abraxane in this study was approximately 50 percent higher than the planned dose for Taxol in this study, however, we were able

to give more cycles of Abraxane than Taxol, a median of 6 versus 5.

The percentage of planned dose was identical in the two arms, 98 percent, and the mean paclitaxel dose intensity was, for the delivered amount of drug, 50 percent higher for Abraxane than it was for Taxol. So not only could we plan to give the dose, but we were actually able to deliver the dose with a comparable tolerability for the patients.

[Slide.]

If you look at the overall toxicity for the two regimens, and this is all toxicities, and the worst grade that a patient experienced for any toxicity is plotted then on this curve, we feel that overall, the toxicity profiles for the two drugs are comparable. They certainly are different, but the overall toxicity profiles are comparable.

There is a higher incidence of Grade 4 toxicity associated with Taxol, and I will go into that in a little bit.

It is also instructive to look at the toxicity after 4 cycles, which is more relevant to the adjuvant setting, and, as expected, the frequency of Grade 4 toxicities is less.

These are data from the first 4 cycles of patients receiving either Abraxane or Taxol. Patients who had progressed prior to 4 cycles are excluded from this analysis, so this truly reflects patients who would be eligible to receive drug without progressive disease.

[Slide.]

Now, I would like to first address some GI toxicities, because these are relatively minor from a clinical perspective, although they were statistically different in our Phase 3 trial.

The nausea and vomiting associated with Abraxane were greater than that associated with Taxol on this trial. The p-values are shown on this slide. However, most of the toxicities were Grade 1 and 2, and we feel that the differences are explainable by the dexamethasone premedication that patients received prior to the Taxol. No standard

premedication was given to the patients receiving Abraxane.

With respect to diarrhea, this is a known taxane toxicity, and again diarrhea was more frequent in the Abraxane arm, however, the incidence of Grade 3 diarrhea was not high in either arm, so the differences really resided in the Grade 1 and 2. This is probably related to the higher paclitaxel dose that is administered.

[Slide.]

Now, I would like to turn to the toxicities that are more clinically troublesome.

Neutropenia on this study was greater for Taxol than it was for Abraxane even though 50 percent more paclitaxel was being administered to the Abraxane patients. This was highly statistically significant and was true whether you looked at all-grade toxicity or just focused on Grade 4.

The reason for this difference is not yet clear. We think it must relate to the presence of Cremophor in the Taxol formulation, but the precise

mechanism has not yet been elucidated.

In addition, hypersensitivity reactions were greater for Taxol than they were for Abraxane even though the Abraxane patients did not receive premedication prior to their treatment. Fortunately, however, hypersensitivity reactions were not a major problem on this study. There were no deaths from anaphylaxis on the Taxol arm in this study.

With respect to peripheral neuropathy, because the dose of paclitaxel was higher in the Abraxane arm, the frequency of peripheral neuropathy was greater on the Abraxane arm than it was on the Taxol arm.

[Slide.]

The improvement, though, from Grade 3 neuropathy to either Grade 1 or Grade 2 was relatively rapid at a median of 22 days. This permitted resumption of dosing in 10 out of 14 patients who remained on study. Their dose was held, and then they could resume dosing at a lower Abraxane dose.

[Slide.]

I would like to focus on our preliminary data from an adjuvant pilot study that we have conducted.

[Slide.]

This was a study done by US Oncology. It involved a dose-dense regimen of AC x 4 followed by Abraxane x 4 cycles. All cycles were given every 2 weeks in contrast to the every 3 weeks that was used in the metastatic trial.

The Abraxane dose was 260 mg/m2, 30 patients received AC, and 29 went on to receive Abraxane; 27 out of 29 patients, or 93 percent, completed all 4 Abraxane cycles, and this is comparable to the dose administered in the Craig Henderson trial, which you will here about later.

The mean cumulative dose of paclitaxel in this setting was 962 mg/m2, significantly higher than the 700 mg/m2 that is possible now with Taxol in the adjuvant setting.

The drug was well tolerated without any unexpected toxicities, and in this study,

peripheral neuropathy was prospectively monitored and followed to resolution. Twenty-eight out of 29 patients, or 97 percent, were asymptomatic 8 months following treatment.

[Slide.]

This study demonstrates on the y axis the proportion of patients who were asymptomatic plotted versus time. At the end of treatment, following the last Abraxane dose, 60 percent of the patients were asymptomatic at the end of the treatment.

By 2 months following treatment, 75 percent were asymptomatic, and again by 8 months, 97 percent were asymptomatic.

[Slide.]

We are doing a number of adjuvant trials in the breast cancer setting. To follow up this study, we are currently doing a trial with US Oncology. John Pippen is the principal investigator. This is a randomized trial comparing dose-dense AC followed by either dose-dense Taxol or dose-dense Abraxane. This study design, though,

is complicated by the inclusion of bevacizumab in both arms.

A number of investigators are also exploring the use of Abraxane in adjuvant regimens that have been standardized using the Taxol formulation. These regimens include dose-dense regimens and regimens incorporating the use of bevacizumab and trastuzumab.

[Slide.]

I would now like to just discuss briefly the proposed comparative safety study using the approved dosing schedules of Abraxane and Taxol. The objective of the safety study would be to describe the safety profiles of Abraxane and Taxol in the adjuvant breast cancer setting following 4 cycles of AC.

As we indicated in the briefing document, Abraxane is committed to conducting such a study. We understand, however, that the final design needs to be agreed to with the FDA.

[Slide.]

So, in summary, one of the questions that

is before you is how similar or dissimilar are Taxol and Abraxane.

Clearly, the active ingredient in both drugs is the same, paclitaxel.

The are administration differences, which are related to the presence of the Cremophor hypersensitivity reactions associated with Taxol, requiring premedication with steroids and specialized IV tubing and prolonged infusions. These are not an issue for Abraxane.

The differences in pharmacokinetics are due to paclitaxel sequestration by Cremophor, affecting the linearity of the pharmacokinetics in the distribution phase of the drugs.

Removal of Cremophor permits a 50 percent higher dose of paclitaxel than that of Taxol, and this increased dose can be safety administered to patients.

Finally, Abraxane has demonstrated higher antitumor activity than Taxol in metastatic breast cancer.

[Slide.]

Having shown you now that removing the Cremophor allows safe delivery of higher doses of paclitaxel, I would now like to turn the podium over to Dr. William Gradishar, who will discuss the data from the Phase 3 metastatic trials.

Results of the Phase 3 Clinical Trials of Abraxane vs. Taxol in Metastatic Breast Cancer

DR. GRADISHAR: Good morning and thank you for the opportunity to present this data.

[Slide.]

As Dr. Hawkins pointed out, the goal of the Phase 3 program was to determine if removal of Cremophor from the Taxol formulation would preserve the efficacy of paclitaxel.

My charge over the next 10 or 12 minutes is really to highlight some of the key preclinical data that demonstrate the superiority of Abraxane over Taxol and then segue to a review of the key observations made from the pivotal trial in patients with metastatic breast cancer demonstrating the superiority of Abraxane over Taxol that Dr. Hawkins alluded to earlier.

[Slide.]

First, the preclinical data, and I think as a summary, what has been demonstrated is that the removal of Cremophor resulted in superior antitumor and intratumor paclitaxel concentrations in preclinical models.

[Slide.]

Experiments that were conducted by Desai and colleagues recently published treated athymic mice with human breast cancer xenografts with equidoses of Abraxane and Taxol.

As depicted on this slide, what is predictable is in control animals not receiving any anticancer therapy, there is rapid expansion of tumor volume.

If you look at those animals that were treated with Taxol, the curves are similar, but there is a delayed growth phase as compared to the animals that received Abraxane where there is basically an ablation of tumor growth.

[Slide.]

To better explain this observation,

similar experiments were done again with athymic mice with xenograft models using equidoses of Abraxane and paclitaxel. The animals were sacrificed at each of the time points depicted on these curves.

What the data demonstrate is that there is approximately a 30 percent increase in the amount of paclitaxel that ends up in the tumor in those animals treated with Abraxane compared to those receiving Taxol.

In data that I am not showing you, but that is available, as opposed to tumor tissue, if you look at normal tissues from a variety of different sites, there is equivalence between the amount of paclitaxel that is present in normal tissues.

[Slide.]

In additional animal experiments depicted here using a variety of different xenograft tumors, colon, lung, ovarian, and prostate, as opposed to equidoses of the two drugs, equitoxic doses of the two drugs were utilized.

As is consistently demonstrated across each of these grafts, the animals that received Abraxane had greater antitumor activity than those receiving Taxol.

[Slide.]

I think that serves as a segue to the randomized pivotal clinical trial that has been alluded to, because many of the observations made in the preclinical setting have subsequently been observed in patients.

This is the Phase 3 randomized trial of Abraxane versus Taxol in patients with metastatic disease that led to the approval of Abraxane and was subsequently published in the Journal of Clinical Oncology last year.

[Slide.]

As you recall, this is the schema of the trial in which patients with metastatic breast cancer were randomized to receive Abraxane over 30 minutes at a dose of 260 mg/m2 without any steroid or antihistamine premedications, or Taxol at 175 mg/m2 over 3 hours with the standard

premedications.

[Slide.]

These are the efficacy data that are derived directly from the paper in the JCO, and I think what is demonstrated consistently as you go across the bar graphs, whether you look at the entire population of patients treated, those patients receiving therapy as first treatment for metastatic disease, or on the far right, those that are receiving therapy beyond first line, second line, or beyond, there is a consistent finding that Abraxane is superior to Taxol in terms of response rate across all the different subsets evaluated.

Therefore, the replacement of Cremophor with albumin enhanced the efficacy of paclitaxel in patients with metastatic breast cancer.

[Slide.]

It should be pointed out that the primary endpoint of this study, as agreed to with the FDA, was the reconciled target lesion response rate, and that is demonstrated in the bar graphs on the immediate left of this graph, and again demonstrate

the superiority of Abraxane-treated patients compared to those receiving Taxol.

If you compare that to the investigator target lesion response rate in the middle, or the independent blinded radiologist target lesion response rate on the far right, again, there is consistency across all of these different analyses demonstrating the superiority of Abraxane compared to Taxol in this study.

[Slide.]

As this was the primary endpoint of the study, it was what was incorporated into the package insert as shown on this slide, and as stated in the insert, Abraxane demonstrates a statistically significant higher reconciled target lesion response rate, 21 percent versus 11 percent, for those patients receiving Taxol.

[Slide.]

These are the time to disease progression curves. As can be seen in this slide, those patients receiving Abraxane had a superior time to disease progression compared to those that received

Taxol.

I should make a few additional comments about these curves. Number one, they are under review by the FDA at this point, and how these data were generated, for the first 6 months, both the investigator analysis was included, as well as the independent blinded radiologist review. Beyond 6 months, it was the investigator's assessment of a response in progression that went into the curves. These remain under review by the FDA at this time.

[Slide.]

The survival curves are equivalent between the two treatment groups.

[Slide.]

Once this trial was completed or actually concurrently, an independent randomized Phase 3 trial was initiated and has completed accrual in China. The design of this trial is completely similar to the trial that I just presented, comparing Abraxane at the same dose with the same caveats about infusion time and premedications compared to Taxol.

With 80 percent of the response data available at this point, you can see that again, those patients treated with Abraxane compared to Taxol had a superior response rate, and if one looks at the subset of patients who are receiving therapy as first-line therapy, the advantage for those receiving Abraxane is a response rate 2.5 times higher than those receiving Taxol, so very similar findings.

[Slide.]

The preliminary progression-free survival is depicted here. Again, I think this demonstrates curves that look very similar to the pivotal trial that led to the approval of Abraxane.

[Slide.]

From the two randomized trials in metastatic breast cancer, we have a consistent finding showing the superiority of Abraxane over Taxol, and I think based on the preclinical data that has been generated, we have an explanation that can be offered.

On the left is a demonstration that 50

percent more of Abraxane can be delivered than Taxol with equivalent toxicity, and secondly, on the right, as I already pointed out, more of the drug paclitaxel actually gets into the tumor.

I think between these two explanations, we have a way of explaining the results that have been observed in both randomized trials that have been conducted to date.

[Slide.]

In summary, I think Abraxane consistently demonstrated antitumor activity that was superior to Taxol in patient with metastatic breast cancer, and there is no scientific reason to believe that Abraxane would be less effective than Taxol in the adjuvant setting.

With that, I would like to turn the podium over to Dr. Hudis, who will provide his perspective on the use of Abraxane in node-positive breast cancer.

Perspectives on the Use of Abraxane
in Node-positive Breast Cancer

DR. HUDIS: Thanks very much and I

appreciate the opportunity to discuss this with the committee today.

What I am going to do is build on the information that has already been presented and add a few more details with regard to the specifics of clinical trials in the adjuvant setting to address this question.

[Slide.]

Firstly, as you have already heard from Mike Hawkins and Bill Gradishar, Abraxane is Cremophor-free paclitaxel, and it is the case that removing Cremophor allows for the safe delivery of a higher dose of paclitaxel, and in metastatic breast cancer, Abraxane has been demonstrated to have greater antitumor activity than Taxol.

What I am going to address specifically now are two more points. Paclitaxel and its generic equivalence, or Taxol and its generic equivalence are approved for adjuvant use already, and the Abraxane dose of paclitaxel is safer and higher than the dose of paclitaxel already approved for use in the adjuvant setting.

Based upon the data that you have seen, and what we will show you, we believe that there is no scientific basis to hypothesize that Abraxane will be any less effective in the adjuvant setting than the approved version of the drug Taxol.

In addition, we will show you that we can safely deliver a higher dose of paclitaxel than that already proven effective in the adjuvant setting and that is already shown to be superior in metastatic disease.

[Slide.]

Now, the basis of the Taxol approval, as you have heard already, is the CALGB Trial 9344, which Craig Henderson first reported in 1998 at ASCO, was updated for purposes of this approval, and subsequently updated again when published in the Journal of Clinical Oncology in 2003.

Consistent with the initial and interim reports, this study shows a reduction in risk of recurrence of 17 percent when Taxol is added after AC, and the reduction in the risk of death of 18 percent.

You will recall that this was 3 by 2 factorial design intended to question both the addition of paclitaxel, on the right, but also the value of dose escalation for doxorubicin, on the left, and, in fact, it did not show any difference for dose escalation of doxorubicin.

I want to also point out that even with this late follow-up now, fewer than half of the patients enrolled on this trial have reached the disease-specific endpoints that would encompass disease-free survival, and this will become relevant later.

Finally, the maximum planned paclitaxel dose on this study of 175 mg/m2 x 4 is 700 mg/m2 total. In fact, 92 percent of the patients on this trial received all 4 doses of Taxol. There were, as well, dose reductions allowed, so we can be confident that less than 700 mg/m2 was actually delivered as a mean cumulative dose.

[Slide.]

Now, if we turn back to the Stage IV, the metastatic breast cancer trial that Bill Gradishar

and Mike Hawkins have already presented to you, I want to focus on a sub-analysis that we can draw out of that trial limited to 4 cycles of treatment.

You will recall in this trial that there were 229 patients randomized to the Abraxane preparation, and there were 225 patients randomized to Taxol. Of those, 179 and 163 were eligible for 4 cycles of treatment because they had not developed progressive disease.

If we then ask, of those patient eligible to receive 4 cycles of treatment, how many actually received it, indeed, it is 92 percent and 93 percent, precisely matching what was obtained in CALGB 9344.

In addition, if we then focus on the cumulative dose of paclitaxel, again reminding you that it was 700 mg/m2 on 9344, in fact, 673 mg/m2 was the actual delivered cumulative dose on the Taxol arm of this trial over 4 cycles, very precisely consistent with what was seen in the adjuvant setting on 9344, and turning to the left, 987 mg/m2 of paclitaxel, as Abraxane, was delivered

with the Abraxane preparation.

[Slide.]

So, what are the issues that we have to consider if we were to approve Abraxane in the node-positive setting without conducting an efficacy trial?

This really boils down to three questions: What are the risks of approving the drug without an efficacy trial? What are the challenges that conducting an efficacy trial would entail? What are the benefits of not requiring an efficacy trial?

I am going to take these three questions one by one.

First, in terms of the risks of approving the drug, could Abraxane actually have lesser antitumor activity than Taxol based on the available evidence?

The second question, could we discover more or different toxicities in the adjuvant setting for Abraxane as compared to Taxol and other taxanes already approved?

Could the higher dose of Abraxane in some way compromise our ability to actually give the full course of 4 cycles of paclitaxel that is already known to be effective in the adjuvant setting?

[Slide.]

Focusing on the first question, could Abraxane have less antitumor activity than Taxol, it is unlikely given the data available in the metastatic setting. Replacing the Cremophor with albumin has allowed the delivery of a higher dose and more effective dose of paclitaxel with comparable tolerability, as you have heard, and this was the basis for the approval of Abraxane in metastatic breast cancer.

Could there be more or different toxicities reported in the adjuvant setting compared to the approved taxanes? Well, there is an extensive clinical experience available with paclitaxel.

The safety profile is well-established from the randomized trial for Abraxane in the

metastatic setting, as well as in other clinical trials, and globally, it is reasonable to say that the solvents required for conventional Taxol are more toxic than the albumin required with Abraxane.

Could the higher dose of Abraxane specifically compromise our ability to actually deliver the full 4 doses of chemotherapy with Taxol already known to be effective in the adjuvant setting?

As I have shown you specifically, there is no evidence from the metastatic trial that there is any decrease in the deliverability of 4 cycles of this drug despite the higher dose and the greater effectiveness.

[Slide.]

I am going to focus now on the second question, which is certainly a core one for us today, what are the challenges that would result from requiring an efficacy trial.

[Slide.]

Very specifically, we have to consider several things. First, a trial that compares two

formulations of an active taxane would consume considerable resources, and that is certainly an important issue globally.

In this regard, ECOG 1199 recently reported at the San Antonio Breast Cancer Symposium by Joe Sparano is instructive and informative.

Based on this, I am going to show you in a moment that there is a very high chance, if we were to compare Abraxane against Taxol in the adjuvant setting, that we would find no difference between the two drugs, and there is a very, very low chance that we would demonstrate lesser activity for Abraxane.

[Slide.]

As a reminder, this is ECOG 1199. In this trial, node-positive breast cancer patients and high-risk node-negative patients were treated with 4 cycles of conventional Q3/week AC, and this was followed by either paclitaxel, in green, or docetaxel, in blue.

In addition, each of the taxanes was given either at a low-dose weekly schedule, comprising as

you see here 12 weeks, or a higher dose conventional schedule, once every 3 weeks, totaling 4 doses. The actual doses planned on the study are shown in the boxes on the right.

[Slide.]

This study accrued over 5,000 patients, it had about 4 years of follow-up, and was reported this winter at San Antonio even though it had not yet reached its protocol-defined first reporting landmark of events.

In other words, there were fewer events than required for the first report, but an analysis of the event rates to that point suggested that there was very little chance that prolonged follow-up would ever allow this trial to demonstrate a significant difference between the arms.

What was seen here was that Taxol compared to Taxotere yielded a hazard ratio that was not significant, 0.985, and Q3/week administration versus weekly administration yielded again a hazard rate that was not significant, 1.043.

This trial highlights a blessing of the recent developments in the adjuvant setting, but certainly a challenge in terms of clinical trial conduct, and that is, that the event rates across the board, across multiple cooperative groups, across multiple years now, have consistently fallen below that which is planned in the studies.

These event rates, we would suspect will continue to fall for reasons shown here. For example, HER2-positive disease, which was enrolled on the ECOG 1199 study to some degree, will, in fact, be removed from the mix, because these patients will be receiving trastuzumab, further suppressing their event rates, and similarly, the more we learn about the benefits of potentially prolonging adjuvant hormone therapy for patients with ER-positive disease, the more likely we are to see a falling event rate in that subset, as well.

So, taken together, these factors predict that whatever event rates we need for our studies, and whatever we expect to see in the future, may, in fact, be discordant.

[Slide.]

So, if we were to conduct an efficacy trial with the following assumptions, here is what results.

Abraxane versus Taxol with a hazard ratio of 0.97, I point out to you that this is double the hazard ratio observed as a point estimate for the two taxanes in ECOG 1199.

The lower bound of the 95 percent confidence interval in this model is 0.89. This maintains 50 percent of the Taxol effect based on the Taxol package insert.

This assumes an event rate of 18 percent, which is 1 percent above the event rate seen in ECOG 1199, all experience right now suggesting that event rates may, in fact, be lower going forward, and an alpha of 0.05 with 80 percent power, which is a standard statistical criteria.

Based on these assumptions, for non-inferiority, we predict 8,644 patients are needed, making this, as far as I know, the largest single chemotherapy trial yet conducted in the

adjuvant setting, and for superiority, we end up with obviously, the impossibility of 190,000 patient study.

[Slide.]

What if we make changes in our assumptions in order to make the trial potentially more feasible?

The first assumption change we make is a wider confidence interval. We set the upper bound of the 95 percent confidence interval for Abraxane versus Taxol at 1.28. This is the inverse of the 0.78 hazard ratio seen in CALGB 9344.

Well, obviously, for non-inferiority, this gives us a potentially feasible study design of 2,560 patients. It is not applicable to the superiority question, but it is important to point out that that wide confidence interval fails to exclude the possibility that Abraxane offers no benefit after AC compared to AC alone.

What if instead of that change, we invoke a larger effect size, so we call the true hazard ratio for Abraxane versus Taxol 0.85? This yields

for us again about 2,600 patients for non-inferiority, about 7,000-plus patients for superiority, but it is important to read on the right here, the clinical implication.

This assumes a treatment effect 10 times greater for Abraxane versus Taxol than the point estimate in ECOG 1199 for Taxotere versus Taxol, a 10 times greater effect.

What if instead of these two changes, we look at a higher event rate, instead of programming an 18 percent event rate, we aim for a 36 percent event rate? Here, non-inferiority grows to 4,272 patients, the superiority design is almost 100,000 patients, and accrual would be very limited because of the smaller number of patients who would fit this poor prognosis profile. In addition, accrual would be prolonged.

I have to point out again this is twice the event rate seen in the node-positive trial recently conducted by ECOG.

Finally, what if we accepted a larger type 1 error, an alpha of 0.1? This yields a

non-inferiority design of 6,778 patients, and, of course, superiority becomes massive again at 150,000, and it yet allows a very large positive error rate.

I want to finally point out that of all these assumptions and results, almost all of them yield chemotherapy trials larger than any yet conducted in the adjuvant setting.

[Slide.]

So, finally, what are the benefits of simply not requiring an efficacy trial for Abraxane versus Taxol?

[Slide.]

Well, this brings us back to the FDA position regarding 505(b)(2). Not requiring a trial would satisfy some of the points that are raised here. For example, we would avoid a clinical trial which might not be scientifically necessary, and we would avoid a duplicative study that would simply slow the process for drug approval without likely yielding a corresponding benefit to the public health.

[Slide.]

More importantly or related to this, we would preserve resources for other research in a time of limited resources and budgets. This is critically important before considering a massive clinical trial to test a chemotherapy question such as this.

Finally, we would make to the public available Cremophor-free paclitaxel as an alternative to Taxol sooner rather than later, and although it is rare, there are occasional deaths in the adjuvant setting where patients are being treated for cure from hypersensitivity-like reactions due to conventional Taxol.

The amount of steroid premedication required would, of course, be reduced since it is not required for Abraxane, minimizing some of the immediate toxicities associated with currently approved adjuvant therapy. As I said already, these considerations are clearly important in a setting where patients are likely to be cured.

[Slide.]

So, in summary, what we have told you is that Abraxane is Cremophor-free paclitaxel, that removing Cremophor allows the safe delivery of a higher dose of paclitaxel than what is already known to be safe and effective in both the metastatic and adjuvant setting.

This paclitaxel dose can be delivered with acceptable tolerability.

In metastatic breast cancer, Abraxane has proven greater antitumor activity than Taxol with acceptable tolerability, and the same degree of drug delivery as is seen with conventional Taxol.

Paclitaxel is, as Taxol and generic equivalents, approved for use in the adjuvant setting.

The Abraxane dose of paclitaxel is safe and higher than what is already known to be effective in the adjuvant setting.

As a result, there is no scientific basis to hypothesize that Abraxane will be less effective as adjuvant therapy because of these factors already spelled out for you.

Thank you very much for the opportunity to present.

DR. HUSSAIN: Thank you, Dr. Hudis.

The FDA presentation will be led by Dr. Patricia Cortazar.

FDA Presentation

NDA 21-660

Proposal for Abraxane Approval in Adjuvant Breast Cancer

DR. CORTAZAR: Thank you. Good morning.

This is a very unusual presentation. We are not here to present FDA's review of a supplemental NDA. I am going to present FDA's concern with Abraxis BioScience proposal for marketing authorization of Abraxane for the adjuvant treatment of node-positive early breast cancer without conducting an adequately sized trial to characterize safety and efficacy.

This is an important issue that will set a precedent on the future approval of new formulations of approved drugs. FDA believes that therapy in the adjuvant breast cancer setting has a

different risk-benefit ratio compared to the therapy in the metastatic breast cancer setting.

Therapy in the adjuvant breast cancer setting is given with a curative intent, and therefore, it should have a well-identified risk-benefit.

[Slide.]

Abraxane is a paclitaxel albumin-bound formulation marketed by Abraxis BioScience.

[Slide.]

It was approved on January 7, 2005, for the same Taxol metastatic breast cancer indication, which is treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

[Slide.]

Abraxane is proposing the following new indication for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing

combination chemotherapy.

[Slide.]

When a marketed drug is off-patent, there are three regulatory pathways for a competitor to bring the drug to market. One is the well-known New Drug Application, which includes full reports of investigations.

A second pathway is an Abbreviated New Drug Application, which is used for generic drugs. Abraxane does not qualify for an ANDA because it is not bioequivalent to Taxol.

The third pathway is called 505(b)(2), and it is named after Section 505(b)(2) of the Food, Drug and Cosmetic Act.

[Slide.]

This regulation pathway applies to new formulations of marketed drugs and authorizes the FDA, where appropriate, to base approvals of new drugs entirely or partially on studies not conducted by the applicant and for which the applicant has not obtained a right of reference or use.

In early discussions with Abraxis, FDA agreed that Abraxane could be compared to Taxol under the 505(b)(2) regulations because the sponsor was developing a new formulation of paclitaxel that promised to be less toxic than Taxol. However, the sponsor was told that clinical studies would be necessary to demonstrate efficacy and safety of Abraxane.

[Slide.]

FDA agreed to use the preclinical genetic toxicology studies from the Taxol application to support Abraxane approval, and FDA also agreed that a study that could support the approval of Abraxane in the metastatic breast cancer setting could use response rate as a comparative measure of Taxol antitumor activity instead of a more stringent standard time-to-event endpoint, and that was because the agents were considered to contain the same active molecule.

[Slide.]

This slide shows the outline for this presentation.

First, I will present Abraxis proposal for approval of Abraxane for the new adjuvant breast cancer indication.

Then, Dr. Brian Booth will present the pharmacokinetics of Abraxane compared to Taxol.

I will summarize Abraxane's basis of approval for metastatic breast cancer.

I will follow with Taxol's basis of approval for adjuvant breast cancer.

We will talk about FDA concerns with Abraxis proposal.

Dr. Rajeshwari Sridhara will talk about the plan to approve Abraxane in the adjuvant breast cancer setting.

We finalize with questions to the ODAC Committee.

[Slide.]

Abraxis BioScience is proposing the following plan for approval of Abraxane for adjuvant treatment of node-positive early breast cancer under a 505(b)(2) regulation.

These two bullets are the 505(b)(2)

components of the proposal.

The first component are the results of the randomized Intergroup study that served as the basis for Taxol approval for the adjuvant treatment of node-positive early breast cancer.

The second component are the preclinical genetic toxicology studies with Taxol.

[Slide.]

This slide shows the components of the proposal, which consists of studies that have been done or are currently ongoing by Abraxis BioScience.

The first one is the comparison of the pharmacokinetics of the Abraxane and Taxol paclitaxel formulations.

The second one are the result of the study comparing Abraxane and Taxol that served as the basis for approval of Abraxane for metastatic breast cancer.

The last is Study CA030, a single arm, 30-patient study of dose-dense AC every 2 weeks x 4 cycles followed by dose-dense Abraxane at a dose of

260 mg/m2 every 2 weeks x 4 cycles.

Note that this study does not have the same dosing schedule as the proposed safety study.

[Slide.]

On March 13, 2006, Abraxis proposed a single arm Phase 2 safety study to support approval of Abraxane for the adjuvant treatment of early breast cancer. The sponsor requested that an efficacy study to support approval of Abraxane should not be required.

FDA did not agree with Abraxis proposal and decided to take this application to ODAC for further discussion.

On July 2006, Abraxis submitted an ODAC briefing draft with a different proposal that consisted of a 400-patient randomized safety study not powered to demonstrate efficacy or safety of Abraxane in the adjuvant treatment of early breast cancer.

On August 9, 2006, Abraxis ODAC briefing package submission showed that the clinical proposal was changed again to a request for

approval of Abraxane without any study of Abraxane and a commitment for a post-approval Phase 4 safety study of unspecified size.

[Slide.]

Considerations on whether the Abraxis BioScience proposal is acceptable concerned how similar or dissimilar the Abraxane and Taxol formulations are and the risk-benefit ratio of our potential dose and potential benefit of approving Abraxane for adjuvant node-positive early breast cancer without an efficacy and safety study of Abraxane in this setting.

It is important to take into account that Taxol prolongs both disease-free survival and survival in this setting.

Therefore, FDA is concerned with the consequences of a potential decrement in disease-free survival and survival in women with early breast cancer.

[Slide.]

Dr. Brian Booth will present the pharmacokinetics of Abraxane compared to Taxol.

DR. BOOTH: Thank you, Dr. Cortazar. Good morning.

[Slide.]

In comparing the pharmacokinetics of Abraxane and Taxol, we should consider the paclitaxel moieties that may be generated by both drugs. Abraxane consists of paclitaxel which is bound to protein particles, namely, albumin. Taxol consists of paclitaxel that is dissolved in the Cremophor solvents.

When you administer Abraxane to a patient, the sponsor hypothesizes that the protein structure disintegrates and produces albumin monomers to which paclitaxel is attached. It is likely that free paclitaxel is also generated, and it is possible that some of the Abraxane may persist, as well.

When you administer Taxol, Cremophor micelles are generated that contain paclitaxel, and there is also some free fraction of paclitaxel that is generated. In these studies conducted by the

sponsor, only total paclitaxel is measured.

[Slide.]

Of the moieties generated, current pharmacological thinking is that the activity of the drug is mediated by the free unbound fraction of the drug in the patient. This also appears to be true for paclitaxel.

In these studies, only total paclitaxel could be measured, and this is problematic because for Abraxane, total paclitaxel may consist of intact drug, albumin monomers paclitaxel, and free paclitaxel.

For Taxol, total paclitaxel may consist of paclitaxel in the micelles, as well as free paclitaxel, so total paclitaxel may not be the same entity for both drugs. Moreover, the most important issue is how much free paclitaxel is generated by each drug, and that question remains unanswered.

Another issue is the biodistribution of paclitaxel to tissues. Often the intention behind the alteration of the formulation of a drug is to alter the distribution to tissues. Such

modifications of the drug are designed to alter the pharmacokinetics of the drug, and by definition this drug is no longer the same as the original

An example of this is Doxil, which is the liposomal formulation of doxorubicin. Both drugs have different pharmacokinetics and clinical indications. In such cases, it is incumbent upon the sponsor to demonstrate that the formulation has altered the distribution of the drug to the tissues in patients, and in the case of cancer, to the tumor.

In the development of Abraxane, no tumor or tissue distribution data in patients were submitted to the FDA, and this question also remains unanswered.

[Slide.]

During the development of Abraxane, the sponsor did studies to assess the pharmacokinetic characteristics of total paclitaxel. One important issue is pharmacokinetic linearity or dose proportionality.

Pharmacokinetic linearity indicates that

the absorption, distribution, and elimination processes are not saturated, and that the concentrations at different doses of the drug are predictable.

Non-linearity indicates that some of these processes are saturated, and the effects of different doses on plasma concentrations are less predictable.

The sponsor demonstrated that for doses of Abraxane ranging from 80 to 375 mg/m2, the AUC of total paclitaxel increased linearly and predictably with dosage. This contrasts with Taxol when it is given as a 3-hour infusion. In this case, it is known that a 30 percent increase in the dosage of Taxol results in a greater proportional increase in Cmax and AUC, and that the clearance of paclitaxel decreases.

[Slide.]

The sponsor also conducted a study directly comparing the pharmacokinetics of total paclitaxel from Abraxane to that of Taxol at Study C008. The pharmacokinetics of Abraxane were

assessed in 14 patients, and that of paclitaxel were assessed in 12 patients.

There are a couple of issues that confound the comparison of these two drugs. First, Abraxane was administered at a higher dosage than Taxol. Abraxane was administered as a 260 mg/m2 30-minute infusion based on earlier dose escalation studies, whereas, Taxol was administered as a 175 mg/m2 3-hour infusion, which is the dosage regimen used in a number of its indications.

Secondly, only total paclitaxel concentrations could be measured.

[Slide.]

This slide shows the unadjusted plasma concentration time curves for Abraxane and Taxol that were observed in Study C008. These data indicate a number of important differences between Abraxane and Taxol.

First, the Abraxane regimen require about a 50 percent increase in dosage to approximate plasma concentrations of paclitaxel derived from Taxol.

Furthermore, paclitaxel from Abraxane at this higher dosage demonstrate the Cmax that was 6.5 times higher than that of Taxol, an AUC that was 17 percent higher than Taxol, and the intrinsic properties of clearance and volume of distribution were 40 and 50 percent higher than that of Taxol, respectively. Based on these data, these two drugs would not be considered bioequivalent.

[Slide.]

This slide shows another way of looking at the same data. Typically, to compare the pharmacokinetics of two similar drugs, the same dose of both drugs would be administered to patients or volunteers preferably in a crossover design type of study.

In order to eliminate the confounding influence of dosage in this case, we can estimate the paclitaxel concentrations of Abraxane by normalizing by dosage. This is possible for Abraxane because the pharmacokinetics are linear.

This slide shows a comparison of the paclitaxel concentrations of Taxol as measured

following 175 mg/m2 dosage compared to concentrations of paclitaxel derived from Abraxane that are adjusted to a dosage of 175 mg/m2.

Under this condition, there is a clear difference in the disposition of paclitaxel between these two drugs .

[Slide.]

This table summarizes the pharmacokinetic parameters that were determined for the Abraxane and Taxol in Study C008. As shown on the left side of the table, at the unadjusted dosage of 260 mg/m2 of Abraxane, it had a Cmax that was 6.5 times higher than that of Taxol. Its AUC was 17 percent higher than Taxol, and its clearance and volume distribution were 43 and 53 percent higher respectively.

After dosage normalization, as depicted on the right side of the table, the Cmax of Abraxane was still 4.4 times higher than that of Taxol, and the AUC of Abraxane was 20 percent lower than that of Taxol.

[Slide.]

In summary, it is unclear whether the Abraxane and Taxol share similar pharmacokinetics because the free concentrations of paclitaxel need to be measured and compared.

Based on the information derived with total paclitaxel measurements, namely, 50 percent higher dose of Abraxane, a higher clearance, a higher volume of distribution, different AUCs, and higher Cmax's, we cannot conclude that Abraxane and Taxol are pharmacokinetically similar.

Thank you.

Basis of Approval for Abraxane for Metastatic Breast Cancer Indication

DR. CORTAZAR: I will summarize Study CA012 to serve as a basis of approval for Abraxane in the metastatic breast cancer setting, because Abraxis wants to use its data to support the adjuvant breast cancer approval.

[Slide.]

Study CA012 was a randomized, multicenter, open-label, Phase 3 trial in 460 women with metastatic breast cancer. It was conducted at 70

sites located in Russia, 77 percent of the patients; UK, 15 percent; and Canada and the U.S., 9 percent.

Patients were randomized to receive Abraxane at a dose of 260 mg/m2 as a 30-minute infusion, or Taxol 175 mg/m2 as a 3-hour infusion.

Fifty-nine percent of the patients received the study drug as a second line or greater than second-line therapy, and 77 percent of the patients had previous exposure to anthracycline.

The study was designed to show non-inferiority in response rate.

[Slide.]

The study population consisted of all randomized patients and the following subgroups, which I would like to point out since we are going to see them in a different analysis.

Forty-one percent of the patients received drug as first line only, 59 percent of the patients received drug as second line or more than second line, and 59 percent of the patients consisted of the Taxol-approved population, which are patients

who have failed combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.

[Slide.]

The primary efficacy endpoint was response rate and was based on the reconciled investigators and independent radiology experts assessment of target lesions through cycle 6.

The study was designed to show non-inferiority in response rate, therefore, the sample size for this study was solely based on demonstrating tumor response effect. Secondary endpoints were time to progression and overall survival. There was no type 1 error rate allocated for time to progression or overall survival analysis.

[Slide.]

This table is extracted from the Abraxane label. The observed response rates were Abraxane 21.5 percent and Taxol 11.1 percent. These results suggest a superiority of Abraxane with respect to the primary endpoint in the whole study population.

The observed response rates were also superior for Abraxane in the Taxol indication population.

[Slide.]

Time to progression was a secondary endpoint. At the time of Abraxane approval, evaluation of the secondary endpoint was neither rigorous enough nor mature enough to support a comparative efficacy claim in this single non-blinded trial. Thus, these results were not included in labeling.

There were comparative labeling claims to Taxol, and they were looked at very carefully.

[Slide.]

An updated time-to-progression analysis was submitted to the FDA on July 21st, 2006. This submission is currently under FDA review. We have the following concerns with this analysis:

The study was not blinded. The independent review of the radiologic findings was only conducted for the first 6 cycles of therapy, and disease progression was not systematically assessed in all patients after completion of 6

cycles of treatment.

In addition, multiple analyses of time to progression have been conducted using different criteria for progression and censoring without adjustments of p-value.

For these reasons, time-to-progression results may not be sufficiently reliable to allow a labeling claim.

[Slide.]

A new analysis of overall survival was submitted to the FDA on July 21, 2006. We have the following problems with these data:

There was no difference in overall survival between the Abraxane and Taxol treatment groups. The hazard ratio, Abraxane to Taxol, was 0.9, and the log-rank p-value was 0.348.

Survival was longer with Abraxane compared to Taxol in this group of patients who failed combination therapy or relapsed within 6 months of adjuvant chemotherapy, however, no conclusions can be drawn from a subgroup analysis where the main analysis was not statistically significant.

P-values are not interpretable since there was no statistical analysis plan to analyze survival in this group. In addition, survival has been analyzed in multiples of groups, and the reported p-values have not been adjusted for multiplicity. Therefore, p-values are not interpretable.

[Slide.]

In addition, results from the survival data submitted in June 2005 showed that in the subgroup analysis of patients who received Abraxane or Taxol as first-line treatment, the trend is in favor of the Taxol patients, hazard ratio of 1.2.

While in the subgroup with second or greater line therapy, the trend is in the opposite direction. This shows the hazard of doing subgroup analysis.

[Slide.]

Abraxane safety data from Study CA012 showed that Abraxane has a different toxicity profile than Taxol, but not a better toxicity profile. The incidence of Grade 3 neutropenia was

similar in both arms, and Grade 4 neutropenia was lower for patients in the Abraxane arm compared to Taxol, 9 percent versus 22 percent, however, the incidence of neutropenic fever was low and similar in both treatment arms, and the incidence of infections was higher in the Abraxane arm, 24 percent versus 20 percent.

Hypersensitivity reactions were fewer in the Abraxane arm compared with Taxol, 4 percent versus 12 percent, and the incidence of sensory neuropathy was greater in the Abraxane treatment arm, 71 percent versus 56 percent for all grades, and 10 percent versus 2 percent for Grade 3.

Abraxis claims that Abraxane patients with Grade 3 sensory neuropathy improved to Grade 2 faster than Taxol patients, Abraxane median time to recovery of 22 days versus Taxol median time of 79 days.

FDA does not agree with this claim. The low incidence of Grade 3 sensory neuropathy in the Taxol arm, you see there is 2 percent, only 5 patients, makes it difficult to compare the

duration of neurotoxicity. Also, the endpoint is subjective and the study was not blinded.

[Slide.]

Gastrointestinal symptoms were more frequent with Abraxane compared to Taxol. Nausea, 30 percent versus 21 percent, vomiting, 18 percent versus 9 percent, and diarrhea, 26 percent versus 15 percent. Asthenia was also more frequent with Abraxane, 47 percent versus 38 percent.

[Slide.]

Because Abraxis proposes to base Abraxane approval for adjuvant treatment of node-positive breast cancer primarily on the results of the Intergroup trial that was the basis of Taxol approval for this use, I will now describe the results of the Taxol study.

[Slide.]

This is a Phase 3 Intergroup study of CALGB, ECOG, NCCTG, and SWOG in 3,170 patients with node-positive breast cancer. After stratification for the number of positive lymph nodes, 1 to 3, 4 to 9, or 10 or more, patients were randomized to

receive 4 courses of cyclophosphamide and doxorubicin followed by either Taxol 175 mg/m2 as a 3-hour infusion every 3 weeks for four additional courses or no additional chemotherapy.

Patients whose tumors were hormone receptor positive were to receive subsequent tamoxifen treatment for 5 years, and patients who received segmental mastectomies prior to study were to receive breast irradiation after recovery from treatment-related toxicities.

[Slide.]

At the time of Taxol approval, median follow-up was 30.1 months. The primary analyses of disease-free survival and overall survival used multivariate Cox models, which included Taxol administration, doxorubicin dose, number of positive lymph nodes, tumor size, menopausal status, and ER status as factors.

Based on the model for disease-free survival, patients receiving Taxol had a 22 percent reduction in the risk of disease recurrence compared to patients randomized to AC alone, hazard

ratio 0.78, and p-value of 0.0022.

[Slide.]

Patients receiving Taxol also had a 26 percent reduction in the risk of death, hazard ratio 0.74, and a p-value of 0.0065.

[Slide.]

In summary, there was an overall favorable effect on disease-free survival and overall survival in the total population. Most of the benefit was in the subgroup of patients with hormone receptor negative tumors where patients had a 32 percent reduction on their risk of recurrence, hazard ratio 0.68, and also a 29 percent reduction on the risk of death, hazard ratio 0.71.

Published updated data, at a median follow-up of 69 months, showed a 5-year relapse-free survival of 65 percent in patients receiving AC alone compared to 70 percent of patients treated with AC plus Taxol.

Overall survival at 5 years was 77 percent in the AC-alone treatment group compared to 80 percent in the AC plus Taxol treatment group.

[Slide.]

So, the main issue is whether Abraxane should be approved for the adjuvant treatment of node-positive early breast cancer without a randomized trial demonstrating efficacy and safety, and based primarily on the results of the randomized study that served as the basis for Taxol approval for this indication.

[Slide.]

Some of the considerations are:

Although paclitaxel is the active ingredient in both Taxol and Abraxane, the Abraxane and Taxol formulations are very different. They have different pharmacokinetics and are not bioequivalent using the tested regimens.

As Dr. Booth mentioned, measurements of free paclitaxel are not available, and it would be very important to further evaluate the differences between the two formulations.

Abraxane does not contain Cremophor. It is given by 30-minute infusion without premedication, while Taxol is given by a 3-hour

infusion and requires premedication.

Abraxane and Taxol toxicity profiles are different. In the comparative trial in advanced breast cancer, Taxol had a higher incidence of neutropenia, however, this does not translate into an increase in febrile neutropenia or infection.

Hypersensitivity reactions were higher with Taxol, while Abraxane had a higher incidence of peripheral neuropathy, nausea, vomiting, diarrhea, and asthenia. This observed toxicity does not translate to the early breast cancer setting. Severity and duration of neurotoxicity in the metastatic monotherapy study cannot be assumed to be similar to the adjuvant population.

[Slide.]

FDA agrees that in the metastatic breast cancer trial, Abraxane had a higher tumor response rate than Taxol.

[Slide.]

FDA believes that in the metastatic breast cancer study, time to progression improvement has not been adequately demonstrated. There was no

type 1 error allocated for time to progression analysis.

Time to progression claims could not be confirmed since there was no independent radiologic experts review after cycle 6. Patients were not systematically evaluated after cycle 6, and in an open-label study, there is a potential for bias in progression assessments.

Therefore, p-values for time to progression analyses are not interpretable.

[Slide.]

FDA believes that in the metastatic breast cancer study, survival has not been adequately demonstrated. There was no type 1 error rate allocated for overall survival analysis.

The sponsor has reported that there is no significant effect with respect to overall survival in the ITT population. Therefore, even if we allocate post-hoc a type 1 error rate of 0.05 for the overall survival analysis, there is no alpha left for testing any subgroup analysis such as the Taxol indicated population when the study has

failed to demonstrate an effect in the overall population.

Furthermore, the sponsor has conducted multiple analyses in multiple subgroups and not adjusted for multiplicity. Therefore, the p-values presented for the overall survival analyses are not interpretable.

[Slide.]

In addition, in the first-line patients, survival trended against Abraxane with a hazard ratio of 1.215.

[Slide.]

FDA believes there is a need for a randomized controlled trial adequately powered for disease-free survival and overall survival to properly estimate the risk-benefit ratio of Abraxane in the adjuvant population.

[Slide.]

Data on toxicity comparisons from the metastatic study may not be appropriate to estimate the toxicity effect of Abraxane in the adjuvant setting where Abraxane would be given following AC.

In addition, long-term implications of neurotoxicity needs to be properly addressed.

[Slide.]

Taxol has been shown to increase both disease-free survival and overall survival in the adjuvant treatment of women with node-positive early breast cancer. There is a 22 percent reduction in the risk of disease recurrence compared to patients randomized to AC alone, and there is also a 26 percent reduction in the risk of death.

[Slide.]

FDA is concerned with the consequences of a potential decrement in disease-free survival and survival in women with node-positive early breast cancer if Abraxane is substituted for Taxol.

Therefore, a randomized, controlled trial to properly evaluate efficacy and safety is needed.

Dr. Rajeshwari Sridhara will talk about some trial design considerations.

Trial Design Considerations

DR. SRIDHARA: Thank you, Dr. Cortazar.

Good morning.

I will be presenting some of the statistical considerations in designing randomized controlled trials for evaluating a treatment for adjuvant breast cancer.

[Slide.]

Specifically, with respect to the drug Abraxane under discussion, there are two questions to be answered - is a randomized controlled trial required, and is it feasible. Dr. Cortazar has just now addressed the question of is it required, and I will be addressing the question of whether it is feasible.

[Slide.]

Regarding history of past approvals for the treatment of adjuvant breast cancer, all approvals were based on randomized controlled trials, and every one of the drugs listed had prior approvals in metastatic setting before getting approval in adjuvant setting.

Also, except for tamoxifen registration study, all the drugs were compared to an active

control in these adjuvant studies. Each of the drugs demonstrated superiority over the comparator.

Of note, anastrozole trial had a non-inferiority hypothesis to compare anastrozole with tamoxifen although at the end of the study, anastrozole demonstrated superiority over tamoxifen.

Among these drugs, Taxol, Taxotere, and Herceptin have shown improvement in overall survival also. As seen here, the study sample sizes for comparison of two treatment arms ranged from approximately 1,300 to 7,000 patients.

[Slide.]

An example, somewhat similar to the current application under consideration was that for Xeloda with 5-FU being the prodrug. Although Xeloda had approval for the treatment of metastatic disease based on two randomized controlled trials, the sponsor conducted a randomized non-inferiority adjuvant study comparing to 5-FU leucovorin to establish efficacy and safety in the adjuvant setting.

[Slide.]

To recap the results presented by Dr. Cortazar of Taxol adjuvant registration study with 3,170 node-positive early breast cancer patients, AC followed by Taxol demonstrated superior efficacy compared to AC alone with respect to disease-free survival with a hazard ratio of 0.78, and 95 percent confidence interval of 0.67 to 0.91. That is, there is a 95 percent chance that the true hazard ratio is within this interval.

Note that the hazard ratio could be as extreme as 0.91, the 95 percent upper confidence limit. In this study, a 70 percent upper confidence limit was 0.83.

In this registration study, it was also observed that the receptor-negative population contributed to most of the efficacy observed in the overall ITT population, and the hazard ratio for disease-free survival in this subgroup was 0.68 with the 95 percent confidence interval of 0.55 to 0.85, a 70 percent upper confidence limit was 0.74.

Of note, this registration study also

demonstrated superiority with respect to overall survival both in the ITT population and in the subgroup of receptor-negative patients.

[Slide.]

For evaluating efficacy and safety of Abraxane, there are two options for designing a randomized controlled trial, namely, to either test a superiority hypothesis or a non-inferiority hypothesis.

If the belief is that Abraxane and Taxol are similar, then, a non-inferiority study is more appropriate. On the other hand, if the belief is that Abraxane is superior, then, a superiority study is more appropriate.

In a non-inferiority trial, there are three aspects that are important to be considered. First, how well we know the effect of the control, is the estimate of the effect based on a single trial or several trials, and what were the sizes of these trials.

Second, how much of the control effect can we afford to give up, for example, can we give up

25 percent, 50 percent, or 75 percent of the effect.

Third, when the control effect is estimated based on limited data, retaining at least 50 to 75 percent of the control effect will likely ensure that the new treatment is better than placebo.

A non-inferiority trial allows to evaluate an effect, but not a comparative effect. In considering a non-inferiority trial, given the uncertainties, any potential benefit with respect to toxicity and/or convenience must be made against potential loss of efficacy.

[Slide.]

In the next couple of slides, I will explain some of the terminology that is used in non-inferiority trial designs. In this design, the null hypothesis is that the hazard ratio of the new treatment to the active control are in this case under discussion.

Abraxane to Taxol is larger than a margin M, and alternative, that the hazard ratio is 1,

meaning the efficacy of Abraxane is similar to that of Taxol, or if Abraxane is slightly better than Taxol, then, an alternative hypothesis with the hazard ratio, for example, 0.95, can be considered.

The margin M is determined based on the estimated active control Taxol effect size and the percentage of this effect that is needed to be retained.

[Slide.]

Non-inferiority implies that the new treatment is not much less effective than the control. Suppose X is the effect size of the active control. For example, as presented earlier, and is reported in the Taxol label, defined estimate of the hazard ratio of Taxol to AC alone is 0.78. This implies an estimate of Taxol effect size is at 22 percent reduction in the risk of disease-free survival event.

The term "percent retention" is the percentage of the control effect size X that is retained. For example, a 50 percent retention of the 22 percent effect size is 11 percent effect

size. In other words, the putative hazard ratio of AC followed by Abraxane to AC alone is 0.89.

Similarly, a 25 percent retention implies a putative hazard ratio of Abraxane to AC alone is 0.945 or not so much better than AC alone.

[Slide.]

There are several methods used to estimate active control effect size. For example, fixed margin approach, synthesis methods such as published by Rothman, et al., and Bayesian methods. Every method makes assumptions that are not verifiable. In the absence of verification, generally, a more conservative method is preferred.

No method is ideal and no one method is endorsed by the agency, and all methods have some limitations.

In the next two slides, to demonstrate a hypothetical example, I have arbitrarily considered an upper 70 percent confidence limit as the estimate of Taxol effect size. This takes into account some of the study variation.

[Slide.]

In this slide, I present a hypothetical example of sample sizes required for retaining 75 percent and 50 percent of the Taxol effect size in the overall node-positive breast cancer patients where the Taxol effect size is estimated as a 17 percent reduction in disease-free survival events or a hazard ratio of 0.83.

As previously presented, one could consider two possible alternative hypotheses, namely, Abraxane and Taxol are similar, or the hazard ratio is 1, or Abraxane is slightly better than Taxol or the hazard ratio is 0.95.

The sample sizes are smaller if Abraxane is expected to be slight better than Taxol. The sample sizes decrease as the percent of effect to be retained diminishes.

[Slide.]

An alternative would be to study in an enriched population. Hypothetically, for example, in receptor-negative patient population where the observed Taxol effect in the Taxol registration study was much larger.

Again considering 70 percent upper confidence limit as an estimate of the Taxol effect size, that is, an effect size of 26 percent reduction in risk of disease-free survival events, sample sizes for retaining 75 percent and 50 percent of Taxol effect are presented in this slide.

For example, to retain at least a 50 percent of Taxol effect, that is, the putative Abraxane effect to be at least 13 percent reduction in risk of disease-free survival events compared to AC alone, and with an alternative that Abraxane may be slightly better than Taxol, a total of 4,687 patients will be required.

Other enriched population, for example, with expected early recurrence even may also be considered. However, in choosing the percent retention, as specified before, given the uncertainties, any potential with respect to toxicity and/or convenience must be weighed against potential loss of efficacy.

[Slide.]

The sponsor believes that Abraxane could be superior to Taxol based on metastatic breast cancer study. Therefore, a superiority trial may be considered where there is no loss of efficacy. In such a trial, the comparator need not contain Taxol as long as Abraxane-containing regimen shows superiority over the comparator arm.

Such a study can also be considered in an enriched population with high reference rates, so that the disease-free survival events are observed in a short period of time.

Two possible sample sizes are presented in this slide. In both the scenarios, it is assumed that the 5-year disease-free survival rate in the comparator arm is 83 percent. The first option, if Abraxane is expected to be superior with a 5-year disease-free survival rate of 86 percent compared to 83 percent, then, approximately 4,500 patients will be required.

In the second option, if Abraxane is expected to be superior, with a 5-year disease-free survival rate of 85 percent compared to 83 percent,

then, 7,200 patients will be required.

[Slide.]

In summary, all approvals in adjuvant breast cancer are based on controlled, randomized studies and all had prior approvals for treatment in metastatic disease. A large study is feasible. Prior approvals in adjuvant studies have been based on 1,500 to 6,000 patients.

Sample sizes for superiority trial may range approximately between 4,000 to 7,000 patients. Sample sizes for a non-inferiority trial is dependent on the estimate of the control effect, population, percent retention, and alternative hypothesis.

A randomized study will provide information on retained effect and safety, unlike the proposed single arm study with 30 patients. In considering trial designs, any potential benefit with respect to toxicity or convenience must be weighed against potential loss of efficacy.

DR. HUSSAIN: Thank you.

Dr. Cortazar.

Important Issues to Consider

DR. CORTAZAR: The following are important issues to consider.

[Slide.]

The pharmacokinetics of Abraxane and Taxol are different. Free paclitaxel was not measured.

Differences in Abraxane and Taxol tumor response rate and toxicity profiles in the metastatic breast cancer study indicates these are two different drugs.

Treatment of metastatic breast cancer has different risk-benefit than adjuvant breast cancer. For the approval of Abraxane as a metastatic breast cancer, a randomized controlled trial was required.

Treatment of adjuvant breast cancer is given with curative intent, therefore, adjuvant breast cancer indications have been supported by large randomized trials adequately powered to characterize the safety and efficacy of a drug in the adjuvant population.

FDA is concerned that the gains with Taxol

treatment in the adjuvant breast cancer setting may not be maintained with Abraxane.

FDA believes that any potential loss of efficacy or degree of uncertainty should be offset by a well-characterized and clinically meaningful gain.

We also believe that current information on Abraxane without a well designed trial comparing both efficacy and safety cannot provide adequate information, and it does not justify the potential loss of efficacy in the adjuvant setting.

Thank you.

DR. HUSSAIN: Thank you, Dr. Cortazar.

We will begin the discussion and the question section for the committee. I am going to request that both the people asking the question and the people responding keep it brief, to the point, please, so that we can accommodate as many questions as possible.

Those who have questions catch either my eye or Johanna's eye. We will put you on the list, and we will acknowledge you, and then you can ask

the question.

Questions from the Committee

DR. HUSSAIN: I just want to ask a clarification from the FDA just for the purpose of the discussion. If this drug were to be approved in the adjuvant setting, that means in any setting Taxol was used, whether it's with Avastin with Herceptin after AC, that would become a fact, they don't have to do any trials to ensure safety in those settings, is that correct?

DR. PAZDUR: I think we would have to discuss that further. It depends on how they write their indication and what they are proposing to us.

DR. HUSSAIN: So, for the purpose of today, it is just replacing Taxol after AC?

DR. PAZDUR: Correct.

DR. HUSSAIN: Thank you.

Dr. Levine.

DR. LEVINE: I have several questions.

On the randomized trial in the metastatic patients, the individuals on Abraxane had more nausea, vomiting, and so forth. It was thought

that perhaps, it was stated that perhaps this was due to the fact that dexamethasone was given on the Taxol arm.

How many patients on Abraxane actually got dexamethasone, as well?

DR. HAWKINS: The number of patients who got dexamethasone for any reason was very low. I don't have the number right off the top of my head, but it is certainly less than 10 percent.

The other thing was that antiemetics of any mechanism of action were given actually fairly rarely on this study. Only 25 percent of the patients in either arm aside from the dexamethasone obviously for the Taxol patients, but only 25 percent of patients on either arm received an antiemetic at anytime in the course of treatment, so 75 percent of the patients received no antiemetic therapy at all.

DR. LEVINE: How many patients got Neupogen on each arm?

DR. HAWKINS: There was very little Neupogen used in this study. It was a couple

percent. It was very, very low.

DR. LEVINE: And no difference between the two arms?

DR. HAWKINS: No.

DR. LEVINE: As far as the neuropathy, two questions on the neuropathy. First of all, how many of the patients with neuropathy on Abraxane required narcotic drugs or how many were treated, and then at a certain point you said that 10 out of 14 of those patients eventually received Abraxane again at a reduced dose.

So, my question is, you know, the claim here is that the Abraxane has a higher dose and therefore, better efficacy, so what was the long-term outcomes of those patients who received the reduced dose of Abraxane?

DR. HAWKINS: The patients who developed a peripheral neuropathy on Abraxane had dose reductions to 220 mg/m2, so they were still receiving more paclitaxel than the highest dose of paclitaxel that could be administered on the Taxol arm.

The second dose reduction that we used in this study was to 208 milligrams, and that was still higher than the 175 of Taxol.

DR. LEVINE: I have two more small ones. One, how do you explain the fact, if, in fact, there was a higher response rate, and so forth, with the Abraxane on that trial, the progression-free survival, overall survival were not different, how do you explain that?

DR. HAWKINS: Well, we actually believe that the progression-free survival was longer on the Abraxane arm. There are some issues vis-a-vis the methodologies that were used, but the progression-free survival data have been consistently favoring Abraxane for the entire population.

There are issues that the FDA has gone into in the briefing document. For the sake of time, we didn't go into those discussions during our presentation. I would be more than happy to spend time focusing on that if that's a key issue for the committee.

DR. HUSSAIN: What I was going to suggest is we get through with the questions first.

DR. LEVINE: I have one more, which is apparently you first came at some point, and I don't know the date here, you came to the FDA with a 400-patient study, so what changed you, what was that 400-patient study, when then you show that this is going to take 12,000, 7,000, what was the 400, what was your thinking?

DR. HAWKINS: Our position all along on this has not changed right from the beginning, and I think as the FDA has accurately noted, we have proposed that an efficacy trial was not required.

We feel that the efficacy of Abraxane in metastatic breast cancer has been documented by the data that we have in the metastatic setting. These are simply two formulations of paclitaxel. This is not comparing Taxol to Taxotere or Taxol to epothelone or anything else. These are just two forms of paclitaxel.

So, clearly, we have never wanted to do and never felt it was scientifically necessary to

do an efficacy study. The very large numbers that both we and the FDA have put up on the screen this morning relate to determining a difference in efficacy, either superiority or non-inferiority design.

Our position all along, though, has been that we should do a safety study to characterize the toxicity profiles of Abraxane compared to Taxol in this adjuvant setting. We initially proposed a 400-patient study. We were having discussions with the FDA as far as the efficacy issue. We never really got to discussing what a safety study would look like, so we have backed off from that.

We do have safety data in the metastatic setting. We do think that that predicts what is going to happen in the adjuvant setting. If anything, it maybe overpredicts the toxicity that will occur in the adjuvant setting.

In our briefing document, we made it clear, I thought, that we are committed to doing the comparative safety study. The only thing that we said our recommendation was given the toxicities

of Cremophor, the risk of death from hypersensitivity reactions, et cetera, that this could be done as a Phase 4 commitment, but it was a recommendation that we stated, and that was all. We have never backed away from doing a safety study.

DR. HUSSAIN: Thank you.

Dr. Swain.

DR. SWAIN: Thank you. I have three questions. One, why was the dose of 260 or how was the dose of 260 mg/m2 chosen for all your trails?

DR. HAWKINS: The MTD of Abraxane is 300 mg/m2, as we demonstrated in our Phase 1 studies. As Dr. Cortazar mentioned, the original trial design was a non-inferiority trial design of Abraxane versus Taxol. That was the original criteria for approval.

As part of that trial design, the Abraxane arm could not be more toxic than the Taxol arm, and so we reduced the dose a little bit from our MTD. As it turned out, Abraxane was superior in that setting, so it became less of an issue, but

originally, it was an issue regarding the non-inferiority trial design.

DR. SWAIN: Thank you. Did you look at the time to resolution to Grade 1 neuropathy in your metastatic trials, as you did with the US Oncology studies?

DR. HAWKINS: The time to improvement of neuropathy on the Phase 3 metastatic trial was not a prospectively defined endpoint in the study, so all we could rely on was the adverse event reporting that we received on the patients during the study.

That was one of the reasons why we did the prospective study with US Oncology.

DR. SWAIN: Finally, why were the PK studies done on whole blood?

DR. HAWKINS: We currently have no indication that there are significant differences between looking at whole blood and plasma, and so we just happened to do them with whole blood. We are doing now subsequent studies that you may be aware of at the NCI using plasma.

DR. HUSSAIN: Thank you.

Dr. Venitz.

DR. VENITZ: I have a question about the comparative pharmacokinetic study that you have, because you kept on pointing out in the background in your presentation, the difference in doses that you are able to deliver.

Looking at the Table 6 in your background material where you compare the actual area under the curve, which measures the amount delivered into the body, the two treatments are very similar. The area is only about 15 percent difference.

So, your argument that you give higher doses, but what you get in the body is about the same within 10 percent. The big difference is in your peak concentration that is about 6.5-fold different because of the short infusion time that you are using.

In my mind, it is not really the dose as much as the short infusion time that is the benefit of the treatment. The reason why I am asking that, how do you explain the differences in deposition in

terms of excretion between the two treatments, that you have a much higher renal excretion on Abraxane compared to Taxol?

DR. HAWKINS: The answer to that is actually a fairly long answer, but there are very definite methodologic differences between the way we measured excretion and the way the Taxol excretion was measured.

The Taxol data in the package insert actually used radiolabeled Taxol, which measured not only the parent compound, but the metabolites. We measured paclitaxel and the metabolites using a cold method assay.

The issue, though, regarding--I want to say something about the issue regarding the comparable AUCs. We believe that the AUC for Taxol is artificially elevated because of the presence of Cremophor in the plasma, and the reason that we say that is that the tissue distribution of Taxol has been documented to be dose proportional, and so the high levels of paclitaxel that are present following the Taxol administration don't force more

drug into the tissues in a disproportionate manner.

DR. VENITZ: But you haven't measured free concentrations to validate that, right?

DR. HAWKINS: No, although actually, the answer to that question, though, would be you would have to look at tissue levels of the drug. The free drug may or may not predict the tissue levels. It is known that Cremophor actually reduces, higher concentrations of Cremophor actually reduce the free levels of Taxol, but yet, like I said, the tissue levels are not affected.

I think that the best data that we have are with respect to the data that Dr. Gradishar showed, showing improved delivery of paclitaxel to the tumor. Those were serial samples obtained from animals over time, showing a 33 percent increase in paclitaxel delivery with the same dose of paclitaxel. So, the drug is clearly getting into the tumor, and I think that you have to come back to the response rates.

Clearly, our response rates are better, this is not in dispute, and so our response rates

for patients are better, so clearly, the drug is getting to the patient's tumor.

DR. VENITZ: Let me just follow up on that. But at the same time, you have a high incidence, significantly high incidence in neuropathy.

DR. HAWKINS: That's true.

DR. VENITZ: How do you attribute that if what you are doing is you are increasing systemic delivery? You attributed it to the dose when you presented it.

DR. HAWKINS: Well, and I still attribute it to the dose. The Abraxane dose of 260 resulted in a Grade 3 peripheral neuropathy of 10 percent. The comparable numbers for 250 mg of Taxol with respect to Grade 3 peripheral neuropathy are well north of 20 percent.

We have never done a comparative trial, I don't think anybody would want to do a comparative trial of 260 mg of Abraxane to 260 mg of Taxol, but based on all of the available literature, clearly, the peripheral neuropathy rate for Abraxane under

those circumstances, I think would be markedly less.

Could you show me the dose-response curves? Just put this one up.

[Slide.]

On the Phase 3 trial, what we did was we measured the peripheral neuropathy using the NCI-CTC grade every cycle. This is the cumulative paclitaxel dose here along the x axis, and on the y axis, then, is the average grade of peripheral neuropathy.

These are the physician assessments of peripheral neuropathy, and you can see the curve for Taxol here goes out further, because you are getting so much more paclitaxel, but the curves are not statistically different, they are almost right on top of one another with respect to incidence.

The next slide.

[Slide.]

The same thing. We did patient measurements of peripheral neuropathy, essentially the same pattern. We really feel that this is

related to the cumulative dose of paclitaxel that is administered in the Abraxane formulation, but we do feel that there are qualitative differences between the two drugs.

[Slide.]

These are the data, we showed this curve with a 21-day median time to improvement of the peripheral neuropathy. We did on purpose not show this curve, which is the Taxol curve, with a median of 79 days, because we had the same concerns that the FDA mentioned, that there are only five patients in this arm--even though the p-value using a log-rank was statistically significant--there are only five patients in the Taxol arm, and we chose not to show this pattern.

DR. VENITZ: Can I just ask one follow-up then?

DR. HAWKINS: Okay.

DR. VENITZ: If you think that this is dose related, the neuropathy, what about the neutropenia that you actually saw a reduction on?

DR. HAWKINS: We think that the Cremophor

is somehow accentuating paclitaxel-mediated neutropenia, and that could be due to a number of mechanisms. One, in Taxol, the paclitaxel stays in the central compartment, circulating in the intravascular compartment longer, has longer time in contact with the bone marrow.

In addition Cremophor is an MDR inhibitor and could be potentiating the effects of paclitaxel in the bone marrow. The volume of distribution for Cremophor is not sufficient to get into the tissues and probably affect tumor-mediated MDR, tumors expressing MDR, but it could affect MDR expression in the bone marrow.

But like I said in my presentation, the mechanism for that has not yet been determined.

DR. HUSSAIN: Dr. Rodriguez.

DR. RODRIGUEZ: In Slide 31, you demonstrated that there are several ongoing trials that you designate as safety trials, but they, in fact, look to me to be exploratory trials in which you are trying to determine if, in fact, other alternative schedule in dosing in the adjuvant

setting might be more appropriate.

It suggests to me that perhaps you haven't quite come to a conclusion as to how to dose and/or schedule this drug optimally in the adjuvant setting. Is that what I might infer from this slide?

DR. HAWKINS: Let me go over this slide in a little more detail. I rushed through it a bit because of the time constraints.

The first trial here with US Oncology is a follow-up to the study that I presented, the 30-patient study that I presented, and is taking Abraxane to the next level, and actually doing this comparative trial, incorporating bevacizumab, which US Oncology is anticipating being the state of the art question to ask in the adjuvant setting.

This study is using dose-dense therapy, which again is not currently part of the Taxol label in the adjuvant setting and is looking at either Taxol or Abraxane for 4 cycles with bevacizumab.

This is a company-sponsored study, so we

are very interested in obtaining the data from this. This will provide comparative toxicity data versus Taxol, but again is complicated by the presence of bevacizumab in the dose-dense schedule here.

The other four studies that I showed on this slide are actually investigator-initiated studies. These studies were initiated to replace Taxol with Abraxane, and these regimens were developed using Taxol. So, all of these investigators have an interest in these specific regimens.

They have developed them in the past using Taxol, and, yes, now are exploring the replacement of Abraxane in these regimens. But these are investigator-initiated studies, we are certainly very supportive of these studies, but they are not really part of our registrational pathway.

[Slide.]

The registrational pathway is on 32, which was this study.

DR. HUSSAIN: Dr. Hawkins, if you don't

mind keeping your comments brief, so we can accommodate more questions. Thank you.

I have a request for clarification from Dr. Hawkins and another one to the FDA. Just so that our understanding is clear for the committee, the indication that you are requesting Abraxane to be approved in would be in the setting after AC in the adjuvant setting node-positive patients.

As we sit today, there is not long-term safety information available whatsoever. We know the toxicity in metastatic disease, but we don't know any safety after AC, is that correct?

DR. HAWKINS: That is correct. The approval that we would request would be identical to that, that Taxol currently has.

DR. HUSSAIN: But your assertion regarding safety issues, that they are unlikely, and so on, is really based on what you observed in metastatic disease, and there is no data whatsoever, even in the setting of metastatic disease, given after AC, that there is safe profile.

DR. HAWKINS: We have the safety data from

the adjuvant trial that I showed you, and that was actually a more intense situation where we are giving AC for 2 weeks dose-dense, and then followed by Abraxane every 2 weeks, so that regimen is actually very condensed compared to the current Taxol approval, which uses every 3 weeks and the AC is given every 3 weeks.

DR. HUSSAIN: Thank you. I understand, but it is not long-term side effects for safety.

DR. HAWKINS: No, the long-term data that we have are from the metastatic trial where some patients have been treated for 28 cycles or over 2 years with Abraxane.

DR. HUSSAIN: Thank you.

Clarification from the FDA. Can you give us examples of what drugs were approved under the 505(b)(2), that the sponsor is trying to use? This keeps being mentioned, but give me an example of what has been approved.

DR. PAZDUR: I don't know, John, do you have any history of this, since you have been in the agency obviously a long time, or Bob? I don't

recall.

DR. HUSSAIN: What about the sponsor? You are using it as an example, but give us an example of what has been approved, as a matter of fact, other than mentioning the Act.

DR. HAWKINS: Here is our product obviously, Taxol and Abraxane.

[Slide.]

This is the proposed approval. Genotropin was a reference-listed drug for Omnitrope, somatostatin agent, and then premarin was the reference listed drug for Cenestin. These would be two examples of 505(b)(2) approvals. There have not been 505(b)(2) approvals as far as I know in oncology.

DR. PAZDUR: I do not recall of any and that is why I asked my colleagues, but here again, remember the 505(b)(2) component that we took was primarily the preclinical toxicology issues here. We felt that there would be really no need to repeat animal pharmacology because really we are looking at paclitaxel in both areas. That is why in

the metastatic disease setting, we asked for a randomized study.

Here again this is kind of a quagmire of asking for no study to be done in the adjuvant study to be looking at efficacy whereas, in the metastatic disease setting, where obviously you are at a different risk-benefit relationship, one was done, which is somewhat incongruous.

DR. HUSSAIN: Dr. Cortazar, you wanted to make a comment?

DR. CORTAZAR: I would like to say that there are different applications. Some of them are ongoing, so I cannot comment on them, but recently, epirubicin hydrochloride in a different formulation was approved under the 505(b2).

It depends on--each case is special--it depends on how similar both formulations are, and we make determinations on the regulation of how much do we borrow from the other applications depending on the similarity between both formulations. It is not the same for each one, it is a different case.

DR. HUSSAIN: Thank you.

Dr. Harrington and then I think the last question we will take is from Dr. Swain. Dr. Simon, you have a question? Then, we will add you, too.

Dr. Harrington, please.

DR. HARRINGTON: Thank you. A question for the sponsor. If Abraxane is approved with the available information, and becomes a clinical option in the node-positive setting, what information would the sponsor propose to convey about the effect size here where response is no longer an issue? It becomes a clinical option for physicians who presumably are making choices based on anticipated benefit.

So, what information would you propose be transmitted to clinicians about the effect size on time to progression, or survival, or any of those clinical endpoints?

DR. HAWKINS: We would not try to, and I doubt that the agency would let us, but we wouldn't even try to project an effect size based on our

effectiveness in the metastatic setting.

I think that physicians and patients would choose this treatment based on the same considerations they are making now in the metastatic setting, namely, it is a Cremophor-free alternative, it has a higher response rate in antitumor activity in the metastatic setting, and has a different toxicity profile compared to Taxol.

Under some circumstances, a physician and their patient might choose to use Taxol. We want to give them an alternative for a Cremophor-free formulation.

DR. PAZDUR: One does have to write a label for this drug, and obviously, you would be borrowing from the Taxol label as far as the efficacy.

DR. HUSSAIN: Dr. Swain.

DR. SWAIN: Mike, you made a good point in showing that slide about the time to neuropathy, that the patients had a higher response rate on Abraxane, so that is probably why you had more neuropathy.

You broke down all grades, I think in Slide 24, after 4 cycles, all grades of toxicity. Do you have it just for the peripheral neuropathy for the 4 cycles?

DR. HAWKINS: Yes. We didn't include that in the slide set, but after 4 cycles, there was a 5 percent incidence of Grade 3 neuropathy.

DR. SWAIN: What about Grade 2?

DR. HAWKINS: It's in the briefing package. I don't know the number off the top of my head. Somebody will give it to me in just a second.

DR. HUSSAIN: Dr. Simon.

DR. SIMON: The company's Slide 23.

[Slide.]

Could you explain something on there, it says, "Median cycles per patient, 6 for Abraxane, 5 for Taxol." Yet, with both arms of the trial, 98 percent of the dose was delivered?

DR. HAWKINS: Yes.

DR. SIMON: Can you explain that?

DR. HAWKINS: Sure. The difference in the

median number of cycles per patient was a reflection of the time the patients were on treatment. If a patient went off for progressive disease after 5 cycles, for instance, then, they would not be eligible for subsequent therapy.

The 98 percent refers to the planned dose that they could receive in the absence of progression of disease or unacceptable toxicities. On average, the patients getting Abraxane actually received more cycles.

DR. SIMON: I had a couple of questions about the pharmacokinetics. One, my take on it, if you just compare the 175 for Taxol versus the 260, I mean you don't do any dose adjustments.

With regard to AUC, you have a higher AUC for Abraxane, right, except it's accounted for by the higher early peak, that actually, it sort of tails off faster than for Taxol?

DR. HAWKINS: I will put the table up.

I understand the confusion around this. I think that we have high levels for the Cremophor-based form of paclitaxel, because of this

effect of the Cremophor sequestration in the plasma.

The total paclitaxel is measured in plasma, so that includes the Cremophor sequestered paclitaxel. That artificially raises the pharmacokinetics and the area under the curve for Taxol.

With Abraxane, the drug is given over 30 minutes and at a higher dose, and that is why we have a higher peak level, but, yes, the distribution phase is much different for Abraxane than it is for Taxol. The drug doesn't stay in the plasma as long for Abraxane, distributes out into the tissues.

That is reflected in the higher volume of distribution and the higher plasma clearance for Abraxane, but those two calculations are a function of the area under the curve calculation corrected for dose.

DR. SIMON: A final question is why was neither free paclitaxel nor tissue levels of paclitaxel measured to compare to Taxol?

DR. HAWKINS: We are currently measuring free paclitaxel levels in a study we are doing with the NCI, and I was hoping to have those data, but they are not yet available.

In that study, we are looking at both albumin-bound or protein-bound paclitaxel for the Abraxane-treated patients, as well as free drug. In the Taxol patients, we are looking at Cremophor-bound, protein-bound, and free drug.

So, I think we will finally get some data that clearly answers this question. I think it is very, very difficult to do tissue distribution studies in patients. I am not sure exactly what the implication of that is. Certainly doing tissue biopsies following drug administration, I don't think is the standard part of drug development.

What we rely on really is animal studies in this regard, and we have done those studies. We omitted this slide for the sake of time, but we have looked at the comparative tissue levels of Abraxane and Taxol given at equal doses.

Overall, there is not a very large

difference between the tissue distributions of Abraxane and Taxol. Now, granted, these studies are in animals, but in many respects, these studies are easier to do in animals because we can't yet grind up entire organs and measure radioactivity.

DR. HUSSAIN: Thank you.

Dr. Bukowski.

DR. BUKOWSKI: Mike, the time-to-progression data are important because the response data notwithstanding, the important issues are what are the time-to-progression data.

Do you have time-to-progression data for the metastatic disease study that have been verified, that have been looked at, that we can see?

DR. HAWKINS: Put up the first TI-1.

[Slide.]

Let me explain because there is confusion. The FDA has mentioned multiple analyses. Let me just clarify all of that in one fell swoop with a few slides here.

We have two analyses of TTP that have been

conducted. The first one was based only on the investigator response assessments. This was submitted as part of post-approval commitment to the FDA.

They requested at the time of Abraxane's approval in January of 2005, that when the survival data were mature, that we submit those data for survival and time to tumor progression. We did that in June of 2005, but included only the investigator response dataset.

We then, as part of a labeling supplement, which we just submitted a couple months ago, submitted time to tumor progression data based on independent radiology laboratory assessment combined with the investigator response assessments.

We did this to address the agency's concerns about these not being blinded data, but there is no way you could blind this study effectively.

Now, as Dr. Gradishar mentioned, because we couldn't blind this assessment, the investigator

response assessments were reviewed, the radiographs were reviewed by a group in Boston who were blinded to the treatment the patient received, the investigator assessment of response, and what lesions the investigator was following on the films.

So, these radiologists from Mass. General and Sloan-Kettering who were just putting up x-rays in their room, looking and making decisions. These data were submitted as part of the NDA, and are referred to as our independent radiology laboratory response assessments.

A reconciliation of this dataset and the investigator response dataset formed that reconciled dataset that you see mentioned in the package insert, but in an attempt to address some of the concerns about bias, we included both of these datasets, and basically, if a patient progressed according to either one of these datasets, the earlier time point for progression was used. So, we made a conservative algorithm here.

[Slide.]

These are the two curves that were submitted. The time to tumor progression associated with the June submission 2005, which was only investigator reported data, and then the investigator assessment plus the independent radiology review, which was done in July of 2006.

The data analyses are remarkably similar. These curves at first blush look like they could almost be the same curves, the p-values are identical, and the hazard right here is 0.726, here it is 0.721. So, the data are internally extremely consistent and highly statistically significant.

[Slide.]

What is instructive is to look at the blinded independent radiology laboratory assessment on its own. This helps to address the whole issue of bias that could be introduced in evaluating time to tumor progression.

Here, we only have data to 6 cycles, because that was the only time that we felt that we needed to review the data to document the response,

which was the primary endpoint.

But even during the 6 cycles, using the blinded radiology assessment, the time to tumor progression for Abraxane was longer than it was for Taxol, at the 0.003 level.

DR. BUKOWSKI: Mike, I am confused by the blinded radiology review. Did they use the investigator-assessed lesions, or did they actually do a blind review?

DR. HAWKINS: Absolutely totally blind. They did not know what lesions the investigator chose for review, they did not know the treatment the patient received, and they did not know the investigator's assessment of response.

DR. HUSSAIN: What was the absolute difference?

DR. HAWKINS: Absolute difference, the hazard ratio here is 0.5.

DR. HUSSAIN: And in the study, the schedules of assessments were irrespective of courses, they were both similar on both arms irrespective of course given?

DR. HAWKINS: Both treatments were given every 3 weeks, and the time points for assessment were the same on both arms.

DR. HUSSAIN: I understand, but they were irrespective of the courses, meaning that if somebody got a neuropathy and their course 3 was delayed, and if the assessment had to come after course 3, then, that obviously could give a bias of a longer time to progression.

DR. HAWKINS: We haven't seen any difference in the assessment times in that regard.

DR. HUSSAIN: I believe Dr. Cortazar had a comment, and then that will conclude this morning's session.

DR. CORTAZAR: My comment is that for a time-to-event endpoint to be reliable, it has to have systematic assessments. That is the main problem we have with the data, that we don't see any systematic assessments on patients after cycle 6. It comes to the point that we don't think it might be reliable.

DR. BUKOWSKI: So, patients were not

assessed after cycle 6, is that correct?

DR. HAWKINS: No, that is not correct. After cycle 6, patients who remained on therapy had tumor assessments every 2 cycles.

DR. CORTAZAR: What I understand is that not all the patients were assessed the same after cycle 6.

DR. HAWKINS: There was variability once patients came off treatment as far as the timing of the assessments, that is correct, but as long as they were on treatment, there was standard assessments, just like you would do in a clinical trial.

DR. HUSSAIN: Thank you very much. We will conclude this morning's session. I would like us to come back at 10:40, please, so we can begin the final session of this morning. Thank you.

[Break.]

Open Public Hearing

DR. HUSSAIN: In advance of the public hearing, I will be reading the statement.

Both the Food and Drug Administration and

the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

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

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from

speaking.

Thank you.

MS. CLIFFORD: Our first speaker is Terri Jones.

MS. JONES: I appreciate this opportunity to speak on behalf of patients today. Expanding the use of Abraxane is important for oncology patients. Paclitaxel has proven to be a drug that improves patients' response and overall survival, however, in its current approved form for adjuvant breast cancer, there are many side effects that impact the patients quality of life.

Patients receiving Taxol must be aware of the potential hypersensitivity reactions. In order to receive Taxol, the patient must be premedicated with an antiemetic dexamethasone, diphenhydramine, and a H2 blocker, such as Zantac or Tagamet, to prevent a hypersensitivity reaction.

In spite of these premedications, 20 to 40 percent of patients still have a hypersensitivity reaction. While usually manageable, these reactions cause great anxiety to the patients and

their families during an already stressful time as most reactions occur during the patient's first treatment.

Abraxane can be given without all these premedications because most patients react to the solvent Cremophor, not the drug paclitaxel. This decreases the patient's anxiety about the reaction and it also leaves the patient not feeling so lethargic after their treatment.

Grade 3 and 4 neutropenia places patients at a higher risk of infection that can quickly develop into septicemia. Grade 3 and 4 neutropenia is seen less frequently in patients treated with Abraxane than those treated with Taxol.

Peripheral neuropathy is a side effect that significantly impacts the patients' quality of life. Patients often tell us how the burning, stinging, and numbness in their hands and feet affect their daily lives and while Abraxane does cause peripheral neuropathy, it resolves much quicker than that seen with the Taxol.

In my clinic, per our protocol, we give an

antiemetic and a low dose dexamethasone IV as premed for Abraxane, and patients report minimal, if any, nausea and vomiting associated with their Abraxane treatment.

As an oncology nurse administering chemotherapy, Abraxane is easier to give. Patients do not have to receive the premedications and non-PVC tubing and a filter is not required, and it takes only 30 minutes to infuse.

Taxol given every 3 weeks or every 2 weeks is given over 3 hours. With the additional time of premedication, patients may be in the clinic for 4 to 5 hours on treatment day. This time factor is both inconvenient and difficult for patients and their family members.

The primary goal of oncology nurses is to manage our patients' side effects in order to improve their quality of life while they undergo treatment. Anytime we have a drug that is proven effective with fewer side effects, we need to have that drug available to our patients.

On behalf of my patients and oncology

patients nationwide, I ask that you approve Abraxane to be given to patients for adjuvant treatment of breast cancer.

Thank you.

DR. HUSSAIN: Thank you, Ms. Jones.

MS. CLIFFORD: Our next speaker is Carolina Hinestrosa.

MS. HINESTROSA: Good morning. I am Carolina Hinestrosa. I have not received any financial support from any person or company to be here today, and my organization receives limited support from pharmaceutical companies, and that information is available.

So, good morning. I am Carolina Hinestrosa. I am a mother, I am a two-time breast cancer survivor, I am a health economist, and I am the executive vice president of the National Breast Cancer Coalition.

I am pleased to have the opportunity to testify before ODAC about the importance to consumers of preserving the scientific rigor in clinical research, and the role of clinical trials

as we seek to find real answers about cancer and translate them into real prevention and real cures.

The National Breast Cancer Coalition has been fighting for improvements in breast cancer research including clinical trials since its inception in 1991. NBCC works and the philosophy of evidence-based health care, we, scientists, clinicians, regulators, manufacturers, consumers, and society need to learn what really works for women with, and at risk for, breast cancer, and at what cost both in terms of side effects and harms associated with interventions and increasingly at what financial cost.

Intervention must be based on high quality evidence and appropriately designed randomized clinical trials are the gold standard to obtain evidence of both benefit and harm.

The National Breast Cancer Coalition is concerned about the proposal before ODAC today to bypass clinical trials of Abraxane in the adjuvant setting, and instead use existing data on paclitaxel to form the basis for approval of its

indication in women without metastatic disease.

This proposal would make it impossible to assess in an appropriately controlled way what the long-term safety and efficacy profiles of Abraxane would be, and that is a risk we should not take.

As a survivor and as an advocate, I struggle with my frustration over this low pace of discovery of truly innovative approaches in breast cancer against the push to bring new interventions to market before we know whether and how they will benefit women.

The breast cancer statistics, over 200,000 new cases each year and close to 40,000 deaths are a sobering reminder that we have a long way to go, however, we must use the tools and proven methods we have at hand to systematically assess the potential benefits and harms associated with these interventions.

As a cancer patient, I have learned that all interventions have side effects short and long term, and I expect that this body, the Food and Drug Administration, will enforce the highest

standards of quality in clinical research to make sure that these are fully assessed as it makes its decisions.

I have a problem with the fact that in cancer, we have a high tolerance for risk and side effects of treatments relative to other diseases. I realize that the drug under consideration tries to address both efficacy and side effects and have limited data in the metastatic setting, however, in the adjuvant setting we cannot accept, I cannot accept the even higher level of tolerance for risk that is commonly accepted for interventions in the metastatic setting.

The population of patients in both groups are different and we must obtain the long-term data on both efficacy and safety to truly serve the best interests of the patient population.

Needless to say, we must scrutinize each intervention and more so those that claim to impact patient outcomes in innovative ways. We must find out whether those outcomes are meaningful and real.

Thank you.

DR. HUSSAIN: Thank you, Ms. Hinestrosa.

MS. CLIFFORD: Our final speaker this morning is Ms. Helen Schiff.

MS. SCHIFF: Good morning. My name is Helen Schiff. I am speaking today on behalf of the Center for Medical Consumers. I am a breast cancer survivor and an advocate. I have no conflicts of interest to report and have paid my own expenses.

Before I begin, I would like to point out a problem associated with releasing the briefing documents only 24 hours in advance of an ODAC meeting. This is really too short a period of time for most advocacy organizations to prepare a presentation.

Organizations, such as SHARE, in New York City, which is a breast and ovarian cancer advocacy and support organization, of which I am a member, needs more than 24 hours notice to develop a position that represents the views of its membership. I hope in the future, we will have more time.

But even given the short amount of time, I

felt compelled to weigh in on this precedent-setting decision. As an advocate, I try to hold positions that are in the best interest of all women with breast cancer, not just what is best for me or for someone I know.

We are concerned, not only what is best for those who have breast cancer today, but also for those thousands who will be diagnosed with breast cancer in the future. Looking at it from that perspective, there is no doubt in my mind that it would be a mistake to approve Abraxane for use in the adjuvant setting without testing this drug for efficacy and safety in comparison with Taxol in the adjuvant setting.

Why do I think this? The most important reason is that advocates want treatments based on evidence. We also want new treatments fast, but we don't want shortcuts that might compromise the evidence. We have had too many bad experiences with trusting what appears to make sense.

A lot of experts told us that high-dose chemotherapy would be better than standard dose,

and that is an example actually where a high dose didn't make a difference. Also, as Dr. Hudis pointed out, in the CALBG trials, the high dose of Adria didn't make a difference compared to the normal dose of Adria.

The FDA is mandated to approve drugs that are at least not inferior to the standard of care, and as I am sure you understand, advocates really only get excited about drugs that show an actual clinical benefit, the larger the better.

All you have to do is look at Doxil and Xeloda to see that changing the way a drug is delivered can make an important difference in both efficacy and toxicity. Doxil is doxorubicin, better known as adriamycin. encapsulated in a pegylated liposome. The pegylation tends to keep the drug stuck in the tumor and out of circulation.

Xeloda is 5-FU formulated in a pill form instead of being given as an infusion, and it is metabolized mainly at the tumor site. Both have very different side effect profiles in the original chemotherapies that they are based on.

We know from the comparative metastatic trials that the toxicity of Abraxane and Taxol are not the same either. While Taxol caused more neuropathy and hypersensitivity reactions, Abraxane caused more peripheral neuropathy, nausea, vomiting, diarrhea, fatigue, and weakness.

Of course, Abraxane does not require premedication, which avoids a not insignificant toxicity that is caused by, for some, that is caused by dexamethasone.

It is important for patients with primary breast cancer, who are weighing the risks and benefits, to have trial results in populations of patients like themselves, so that they can make informed choices about treatment, and there may be other as yet unknown issues regarding efficacy that may have not emerged because Abraxane has been studied in so few women.

For example, although Doxil is much less cardiotoxic than doxorubicin, there has been concern about what the interaction will be when it is used in combination with other drugs in the

adjuvant setting.

Clearly, this is the kind of concern that would need to be investigated in a clinical trial prior to its approval in the adjuvant setting. Abraxane, like Doxil, was only used as a single agent in the metastatic setting, and it is not known how it will work in combination with other drugs that it will be used with in the adjuvant setting.

We want to make sure that inferior drugs don't start creeping into the standard of care. We want to make sure that newly diagnosed women have the very best shot at preventing a recurrence, and of not dying of breast cancer.

It is important to remember that a therapy in the adjuvant setting is curative for some women. We want to increase the number who survive, not decrease it. The stakes are very high.

Once a drug becomes standard of care, it can be used as the comparator arm in a registration trial. This is an advocates worst fear, if the drug in the comparator arm is inferior to another

drug that is already in use, then, you can end up replacing it with another inferior drug.

While this is not central to the FDA, advocates also try to ascertain how certain policy decisions impact the future of drug development. A decision to allow reformulated drugs with different delivery systems to skip adjuvant trials encourages the pharmaceutical industry to shift investments from developing more novel agents to developing different delivery systems for already existing chemotherapy drugs.

It is easier and much cheaper to do, and they will come to market much faster if you can skip the adjuvant trials. I am afraid that being able to secure new indications without conducting trials in large adjuvant markets could create an irresistible incentive for industry, while making the risky pursuit of novel agents even more problematic than it is.

In addition to these considerations, I think it is important to be aware of just how weak the Abraxane data is in the metastatic setting. No

time-to-progression or overall survival benefit has been established. All we see is the doubling of tumor shrinkage, and tumor shrinkage has not been proven to correlate with time-to-progression or overall survival in the adjuvant setting.

I want to conclude by putting on my patient hat. What if Abraxane is approved for adjuvant treatment without any further trials, and let's say I have just been diagnosed with Stage II breast cancer. I am eager to hear what my oncologist recommends.

Much to my surprise, he offers me a choice. This happens a lot. You could have adriamycin and Cytoxan with Taxol, or adriamycin and Cytoxan with Abraxane. So, naturally, I ask him which drug will be the greatest assurance that my cancer will not return. His answer to me currently is we don't know.

Taxanes will probably be in use for a long time to come. Will doctors always have to say we don't know, and will they have to say we don't know to all the newly formulated drugs that come on the

market. I certainly hope not.

DR. HUSSAIN: Thank you, Ms. Schiff.

On behalf of the committee, I really want to extend my thanks to all the public hearing speakers for coming her, for your commitment, and for sharing with us your insights and your experiences. We value them always.

Further Questions from the Committee

DR. HUSSAIN: We will go now to another session of questions and answers, and as before, please let us know if you wish to speak. We will acknowledge you with that, and I know that Dr. Carpenter had indicated in the break he had a question, so, Dr. Carpenter.

DR. CARPENTER: It seems to me that the information is reasonably clear on response rates, although the response rates cited, milligram for milligram, are probably not greatly different with these drugs.

There are Taxol studies at 250 mg/m2, which have approximately the same response rates as the 260 with this drug., but the problem is that nobody

knows what response rate means as far as how we ought to translate it into an edgement setting.

The biggest hint we give here about control of disease in any kind of comparative way is the time-to-progression information. I am curious as to we have seen a couple of projected curves, but I have no idea of how many event points and how many measurements were done, and what information actually goes into the formulation of those curves.

I wonder if either the sponsor or the FDA has information about how reliable the disease assessment really was after the primary endpoint and whether it's similar in both arms, and how many people we have lost information on.

I would like to know a little bit about what the quality is of the data that goes into those curves, because that's the only thing that gives us a hint about disease control, and it's longer disease control that this discussion is really all about.

DR. HUSSAIN: Dr. Hawkins.

DR. HAWKINS: The first way to address that is to look at the blinded data that I showed at the end of the last discussion on this issue. Those data I think everybody would agree are the most rigorous dataset that we have.

Those data were from the blinded radiology assessments, so they are completely unbiased in that regard. The problem with those data, though, as noted, is that they are only through 6 cycles of therapy. But it is important to note that the investigator assessments of response during that time, the conclusions of the investigator dataset were confirmed by the independent radiology dataset during that same time period.

We have no reason to believe a priori that the investigator assessments are somehow skewed based on that review during the first 6 cycles.

During the time patients were on therapy, response assessments were done in a very consistent manner. After cycle 6, they were done every two cycles, and we have very good consistent data on that.

The area where I think that the agency has concern is that when patients went off therapy, there was some variability as to how frequently they were assessed for progression at that time, and we have not done analyses that I can show you in that regard, but I can tell you that based on the comparative data that we have up to 6 cycles, the investigator data do seem to be an accurate reflection of what is really going on, and the data then after 6 cycles do rely solely on the investigator assessments of response, but we detected no bias during those first 6 cycles.

DR. CARPENTER: But it's the time after the 6 cycles that I am primarily concerned about.

DR. HAWKINS: It's not actually the time after 6 cycles, because--well, maybe it is--but response assessments were done on a regular basis after that while the patients were on treatment. I think that the variability in the assessments comes in after the patients went off treatment, if they had not progressed when they went off treatment.

DR. CARPENTER: Do we know how many people

came off treatment for reasons other than progression?

DR. HAWKINS: Do you have that?

SPONSOR: About 50 percent.

DR. CARPENTER: Fifty percent.

So, that's a big cohort.

DR. HUSSAIN: Dr. Cortazar.

DR. CORTAZAR: Again, these data are currently under FDA review, so I cannot give you exact numbers, but we look into the data, we look at the sponsor's analysis, and the problem we have is that after cycle 6--the first cycle 6, you have the investigator's report assessment, and you have the independent radiology review.

After cycle 6, you only have one, which is the investigator's, you don't have the independent radiology experts' assessment, and we don't see any consistency after cycle 6, and when you have a time-to-event endpoint, you know, if it is not systematically assessed, you start thinking, I mean how reliable is this data.

I mean if it was not planned to be done,

and following exactly the same on both arms, you know, you really don't know what you are dealing with.

DR. HUSSAIN: Any other questions or issues? Dr. Davidson, do you want to make any comments?

DR. DAVIDSON: I would like to ask maybe Dr. Hawkins and the FDA, as a statistically challenged individual, I was pretty impressed by the difference in the putative trials that might be out there to test this in the adjuvant setting, the numbers that were given by Dr. Hudis in CP-13 and--I am sorry--14 and 15 in your presentation, the numbers given by the FDA are pretty different.

Could you help shed some light on that for me?

DR. HAWKINS: Could you put up the assumption slide, the one before this?

[Slide.]

When you do these trial design calculations, it obviously all lies in the underlying assumptions that you make for the

treatment effect, and as we indicated, in our assumptions we were using a hazard ratio of 0.97. This was twice the difference between Taxol and Taxotere on the E1199 trial, so we felt that was a reasonable assessment to postulate the true hazard ratio for the two drugs.

In some of the slides that the FDA presented, they postulated hazard ratios which were considerably smaller than this, at the 0.8 or 0.85 level. We indicated that we thought that was--in our slide prospectively, without knowing what they were going to present--thought that postulating a hazard ratio of 0.85 was unrealistic, because that's 10 times the difference between Taxol and Taxotere on the ECOG 1199.

Now, you could argue that maybe the hazard ratio should be 0.95, you know, you can discuss that, but these ultimately are two forms of paclitaxel, and you compare Taxotere and Taxol, which we thought was the most relevant comparison, that hazard ratio of 0.985 is very sobering, that's almost 1.

The lower bound of the confidence interval, I think we both agree, both the FDA and we agree that a lower bound that maintains 50 percent of the Taxol treatment effect would be a reasonable lower bound.

The agency mentioned that you could require 0.75, maintaining 0.75 of the treatment effect, in other words, three-quarters of the treatment effect. That would raise the number of patients required rather than reduce the number. They did indicate, though, that the 50 percent retention would be acceptable, and this has certainly been used in the past, so I think that there is less difference along those lines.

The slides went by fairly quickly, but as I was doing calculations, I think that there are some big differences in the event rates in some of the slides. I was trying to figure out whether there was a consistent estimate of the event rates on the FDA slides, and like I said, it was going by fairly quickly, but I think some of these event rates are in excess of 30 percent, and we showed

during our presentation that to do that, you obviously have to restrict your accrual to a very, very narrow subset of patients with a very, very poor prognosis these days.

I think that we are all in agreement with respect to the standard statistical criteria. I think that the variability here comes in estimating the event rate and then also what is a realistic and reasonable assumption for the true hazard ratio between the two drugs.

Again, given the fact that these are two forms of the same drug, paclitaxel, we feel that postulating hazard ratios of 0.8 or 0.85 is not appropriate.

DR. HUSSAIN: Dr. Sridhara.

DR. SRIDHARA: I think what I presented was not described accurately here just now. Our assumption was also that the hazard ratio for Abraxane to Taxol was either one similar, or the other alternative that I considered was 0.95.

What was considered as the Taxol effect was 0.83 or, you know, 0.85, and so on. So, this

was AC plus Taxol to AC alone, so in order to assume what is the Taxol effect size, they have used a lower bound 95 percent confidence interval, which is the total extreme of the effect that one could assume based on that trial, and I took a 70 percent confidence interval.

There are different methods like you can use just the point estimate, which was 0.78, or you could use anywhere between that point estimate and the upper 95 percent confidence interval. The actual estimate, we don't know. That is why it is called an estimate, we don't know the actual effect size.

So, in my case, I chose a different Taxol effect size, but I did not assume that the Abraxane to Taxol, the hazard ratio was 0.85 or 0.83. In the superiority trial, I did assume that Abraxane to any comparator, in this case it doesn't have to be Taxol-containing regimen when we are looking at superiority. There, I did consider it could be 0.85 or 0.87.

DR. HUSSAIN: Dr. Pazdur.

DR. PAZDUR: The real question here is should the trial be done. The regulatory issue of the size of the trial, we will exercise regulatory discretion and flexibility to assure that the trial can be done, and basically, that can be looked at by the percent retention of a non-inferiority study, but I think the real question is should it be done.

Obviously, even Dr. Pazdur isn't going to be asking for a 190,000 patient trial here, let's make it clear, but the trial should, and I think we could look at studies that have been commensurate with other adjuvant trials that are being done, and then take a look at basically what give we could give in some of the assumptions that we are making to make it a realistically sized study.

This is not a new argument that the agency faces with these non-inferiority trials, these trials simply cannot be done. Let me remind you that we had a very similar situation with the capecitabine studies, the Xeloda studies in adjuvant colon cancer, very similar data.

In the metastatic disease setting you had an improvement in response rates primarily, and they took that to the adjuvant setting, did a non-inferiority trial of several thousand patients, had a slight win in the non-inferiority trial with a p-value of about I think 0.06, and that led us to have a lot of confidence that that was a real finding.

Here again, the design of the trial I think is outside of the context of this committee because it really requires a discussion of where a give and take should occur.

Here again, one of the issues that I want to bring up before we go to the questions, if you take a look at the efficacy standard here, obviously, if we look at a 505(b)(2) application, we can, where appropriate, take information from other trials, however that "where appropriate," I think is a very important issue.

If you take really a look at what is being asked for here, in terms of efficacy, the only efficacy statement that is being made is that there

is no scientific reason that Abraxane would be less effective than Taxol, which really equates to downgrading the efficacy standard to there is no evidence that the drug is not effective, which is pretty low.

I think people have to take a look at where they feel where a give and take could occur based on what are the advantages of this drug, and that is really what we are looking for in the committee, what is the advantage of this drug that would want people to take a potential loss of efficacy, and that potential is always there.

All of this information is inferential as far as what the effect would be in an adjuvant setting. One could take a look at this situation and say well, if this goes through, why couldn't take any drug that shows a survival advantage in the metastatic disease say, you know, Dr. Pazdur, we have an improvement of survival in the metastatic disease study by 30, 40, 50 percent, let's skip the adjuvant study, we know we are going to be better, we will just do a safety study. Is

that unreasonable?

DR. HUSSAIN: The word yesterday was "substantial." The word today is "appropriate."

DR. PAZDUR: No, there is still the requirement of substantial evidence.

DR. HUSSAIN: Yes.

DR. PAZDUR: If you go to the 505(b)(2) category, we can rely on the appropriateness of taking that information from the Taxol label and incorporating it into the present label.

What we are doing here with the 505(b)(2) is saying we are taking this Taxol data in the adjuvant setting and moving it over to this Abraxane label.

DR. HUSSAIN: Would that not be misleading?

DR. PAZDUR: I have my opinion, but I do not want to be accused of leading the committee here.

Questions to the ODAC and ODAC Discussion

DR. HUSSAIN: Dr. Perry.

DR. PERRY: Short of asking the

statisticians to engage in a pillow fight to the death, I think there are some practical aspects here that need to be on the board.

If the event rates in adjuvant breast cancer are falling because we are siphoning out patients who are HER2-neu-positive and treating them in a different way, it is going to take a very selected population of patients to go on this clinical trial, if proposed, and it is going to take a long time, at least seven years after the trial is done.

So, add another two years to get it up, seven years to get it done, nine years. Nine years from now, are we going to be interested in knowing whether Abraxane is a substitute for paclitaxel in the adjuvant setting of breast cancer? I sincerely hope not. I hope that we will have found something that would be better than this, and while we are not exactly rearranging deck chairs on the Titanic, we are certainly rearranging something on some kind of ship.

I would like to see this drug approved

simply because I think it's a reasonable alternative, and I would like to suggest that the manufacturer be asked to do a reasonably small, but rapidly completed study to look at the safety to make sure that there is detriment in safety.

But these big studies, 7,000-patient studies, to me, are simply irrational. You couldn't get the patients to sign up to them, I don't think you could get the clinicians to say, gee, here is a really exciting study. I am comparing Coke and Pepsi to see which is the best dark caffeinated cola. There is no sex to this study, and I think it would be hard to sell.

So, I think if you get down to practical aspects, then, I think we ought to consider approving the drug, but requiring the manufacturer to do a safety study of X number of patients, whatever the pillow fight decides, and go from there.

DR. HUSSAIN: Dr. Bukowski.

DR. BUKOWSKI: But the issue is not safety necessarily. The issue is efficacy, and I don't

see the data on efficacy that convinces me that these drugs are the same. That is my concern about this discussion right now.

I think the safety data you can certainly obtain quite easily. I just don't see the efficacy data, and the further discussions we have about the time-to-progression data, the more murky it becomes in terms of really what are they. So, that is my concern regarding this agent.

DR. HUSSAIN: Dr. Simon.

DR. SIMON: There is a lot of kinds of evidence that could potentially be useful between what we have here and doing some 5,000 or 10,000 patient randomized trial.

Now, in terms of a randomized adjuvant trial, you know, in other words, if you restricted the trial to ER-negative patients or patients with lots of positive nodes, the benefit in terms of the size of the effect for Taxol that you gain more than overcomes the fact that you are restricting your patient population, so it is very beneficial if you were going to do that kind of study, to do

it in a high-risk group of patients.

A third of the patients are ER-negative, and the effect size for Taxol in the ER-negative population was much greater than for the ER-positive patients.

But there are also other kinds of evidence. For example, you could do a randomized trial in Stage III patients, and you could do it preoperatively, and then you could actually take the tumor specimens and examine tissue levels of paclitaxel in the patients who had received Taxol versus the patients who had received the drug.

If you were going to actually--what you could do is you could take somebody who was going to do a large adjuvant trial, cooperative group, and was going to use Taxol, and they were going to have some other kind of a randomization to evaluate something, and you could just do a sub-randomization to those patients who were going to get Taxol, you could do a factorial sub-randomization to whether they get Taxol or whether they get this drug.

Therefore, you wouldn't actually be doing a study --you would be utilizing the patients just for this question. So, I think if you wanted to actually be creative about it, there are a variety of things you could do to move us from the evidence that is presented to somewhat more evidence.

Now, I actually view the response rate in the Phase 3 metastatic disease study as meaningful, but not really--not foolproof in terms for predicting whether that indicates you are going to have the same effect in the adjuvant situation.

I am sympathetic to Dr. Perry's point of view, but at the same time I don't really want to see 5,000 patients randomized to answer this question alone, but at the same time, I think just having that comparison of metastatic response rates is not evidence of effectiveness of the drug in the adjuvant setting.

DR. HUSSAIN: Now, in essence, we are in the section where the FDA wants us to discuss the issue, and since the different speakers began discussing the issue, does anybody want to add any

comments? Maybe I can begin.

I guess I don't agree with you, Dr. Perry. The reality of it is, it cannot be driven by absolute numbers. I mean obviously, people did Pepsi and Coke when they did Taxol and Taxotere, and then doing weekly versus whatever the other schedule was, and, in reality, did you really expect that much of a difference, and the end result would fit, that it didn't make that huge of a difference.

I think that approving without--to me, the burden is safety and assured efficacy, and I think everything we heard today, in fact, I am disappointed in knowing that, for example, the published paper in JCO, if I am not mistaken, on the time-to-progression differences, that actually the time to progression was not as rigorously done as I thought from reading the paper. In fact, we are using it to cite something for a prostate trial, and that has kind of shaken my confidence a bit there.

But the point here is that if you cannot

be assured that a woman, after AC, is not going to have more congestive heart failure at five years, for example, there is no data. If you are not assured that after AC, your neuropathy isn't going to be worse, I understand that one can sometimes not comprehend a possibility, but the truth of it, we always get surprised by these things.

I have to also say that responses that don't translate into survival advantages in metastatic disease, there are numerous examples of responses that don't translate into benefit that do make a difference. So, I don't think we could use that in saying that it is safe enough.

From my perspective, I think a study should be done. I think it's to protect patients, it is good science, it is good medicine, and lowering the standard I think would mean tomorrow, some other drug comes in and says I don't really have to do adjuvant trials anymore, I am showing an advantage in metastatic disease.

So, I think you take a risk, and I can't see that, you know, the company obviously has good

connections in other countries. If I am not mistaken, 9 percent only of the patients in the pivotal trial were from the United States. Am I correct? Yes. So, I think a 5,000 trial using Russia, China, a portion from the United States is doable, it is not not doable.

Dr. Simon.

DR. SIMON: I just think we are being a little unfair when we say, well, this would be--I actually don't, I am not satisfied with the evidence for effectiveness or safety of the drug in the adjuvant situation, but I don't think we are being entirely fair when we say, well, if we approve this, then, any drug that shows some effectiveness in metastatic disease setting, you could approve it for adjuvant, because this is a little bit different.

We have Taxol approved in the adjuvant setting, and we have some evidence that this drug delivered in this way, at this dose, has more of an antitumor effect than Taxol, so it's not really just showing some effectiveness in the metastatic

disease setting automatically justifying approval in the adjuvant as a precedent.

DR. BUKOWSKI: But, on the other hand, there are data that suggest the drug is different, the kinetics of the drug are different than Taxol when utilized, and we should look at that also when we try to expand the data to the adjuvant setting.

They may not be the same in that particular regard, so I think we have to be quite cautious when we look at both of these agents. If they were totally identical, and the pharmacokinetics were the same, then, one might have confidence that this would be the case, but it doesn't appear to be the case at the moment.

DR. HUSSAIN: Any other comments?

I think we can go then to the area of the vote. You have the handouts in front of you, and the specific question that the FDA would like us to vote on is:

Should the sponsor conduct an adequate and well-controlled randomized trial of sufficient size to characterize Abraxane's efficacy and safety in

the adjuvant setting?

Do you wish to discuss this question before we go to a vote? Dr. Simon.

DR. SIMON: I actually don't like the way this is phrased because I guess my position is I am not satisfied with the evidence that is presented, but I don't know that I wouldn't be--there might be some intermediate levels of evidence that I might be satisfied with, such as, for example, if I saw a randomized pre-operative trial in Stage III breast cancer showing that levels in the tumor were the same or better for the drug, and showing some benefit, I might be satisfied with that.

But the way this is phrased, it is not asking us whether we are satisfied with the evidence as presented, whether the drug should be approved for the adjuvant setting based on the evidence presented. It is saying should they be required to do a large adjuvant trial.

So, I don't actually like the way this is proposed, the way this is posed.

DR. HUSSAIN: But that is the question

they are asking us.

Rick?

DR. PAZDUR: Why don't we go ahead and answer the question, and people could give their comments regarding their answer.

DR. HUSSAIN: The question, as written, stands, and what I am going to request, please, that you first state your name, a yes or a no vote and briefly, in one sentence, if you are voting yes or no, why.

I am going to begin with Dr. Davidson.

DR. DAVIDSON: Nancy Davidson. I am going to vote Yes for this question, that this trial should be conducted. I think it is because we have been fooled in breast cancer before in adjuvant trials, that what we think is a good idea turns out not to be, and I personally am not prepared to say that we are ready to change the way that we have made the progress that we have made.

DR. CARPENTER: John Carpenter. I am going to vote Yes, and qualify the Yes to say that I think I agree with Dr. Simon and that exactly how

much more evidence is really needed probably should be a matter of discussion, but I think there should be additional evidence particularly on safety and on some kind of comparable efficacy before the drug is approved for this reason.

MS. HAYLOCK: Haylock, Yes. My comment would be that I would hope that FDA and the sponsor can work together and incorporate Dr. Simon's suggestions, and somewhere in between Dr. Simon's suggestions and Dr. Perry's prediction of 9 to 10 years, it seems like there should be some kind of happy medium where a creative, well-designed trial can take place that would not make us a decade waiting for the results.

DR. LYMAN: Gary Lyman. I am going to vote Yes, but I also feel very ambivalent about this. I think the drug has been demonstrated to have reasonable safety and efficacy in the metastatic setting.

I accept their data on time to disease progression in the metastatic setting, and I share Dr. Perry's concern that if we do a very large

confirmatory adjuvant trial, we are going to be asking a question that is really going to be much less relevant a few years down the road given the rate at which we are going.

So, I would second what has been said and Richard's comment that I think what we need here is not a large multi-thousand comparative trial, but something to be worked out to provide maybe data in Stage III patients just to provide additional safety and some evidence of comparable, if not superior, efficacy in an earlier stage setting.

DR. HUSSAIN: Maha Hussain. I vote Yes. I share all the comments that were made by my colleagues. I also think the drug is probably more active than Taxol, and I think it probably will be superior potentially to Taxol, and therefore I think a good trial to answer that question for long-term safety and efficacy is important.

DR. PERRY: Michael Perry. I vote No. I don't think it has to be a randomized controlled trial although I am afraid that the critics of the process will find reason to disagree even with a

Phase 3 study in which there are tissue samples before and after because they will argue that neoadjuvant is not the same as an adjuvant trial, and you can argue this out to nine decimal points in the people who are convinced that only an adjuvant trial is going to be satisfactory, or if they have to get their answer, it will be long after I am off ODAC.

DR. HARRINGTON: Harrington. Yes, for two reasons. One is that I think that counter to Dr. Perry's point that we may have to wait as long as 10 years before the drug is approved, is that we might wind up administering it for 10 years without knowing its real effect.

The other reason I vote Yes, I have confidence that the agency and the sponsor will be able to work creatively and flexibly to create a design for a doable trial. The adjuvant trials that were cited were large, perhaps none of them quite so large as this would need to be, but they were all finished, and they all showed very, very informative information about effect size and side

effect profiles.

DR. LINK: Michael Link. I vote Yes, as well. I think it's a very promising alternative, but even in pediatrics, we have been faked out before with drugs that are active against metastatic disease that don't prove to be active in the adjuvant setting.

I think I would hope that there could be a suitable negotiation or pillow fight or whatever between the sponsor and the FDA to come up with a suitable trial based on some of the considerations that Dr. Simon has provided.

DR. RODRIGUEZ: I vote Yes. Similar reasons have been cited. We also have a responsibility to the patients who expect us to protect their safety and their lives, as well as to not cheat them out of efficacy.

DR. BUKOWSKI: Ron Bukowski. I vote yes. I have confidence the FDA and the sponsor can arrive at a satisfactory design to answer the question.

It could be in a high-risk population

where more events will occur in a shorter time, and I think that is clearly the way all adjuvant trials are going at this point in time, so I have confidence they will be able to arrive at a mutually agreeable proposal.

DR. LEVINE: Alexandra Levine. I vote Yes, as well. I am not comfortable with the progression-free survival data over time and I think that is a critical issue on an adjuvant trial, and even on the toxicity I am not comfortable in the sense that one of the things we are told, for example, is that the Abraxane arm did not have use of Decadron, et cetera, but we are hearing from the community that, in fact, low-dose Decadron is given in the community.

There are questions on toxicity and there are questions on efficacy, and I also hope and believe that there will be a nice way that the two groups can work this out.

DR. VENITZ: Jurgen Venitz. I am going to vote Yes, as well, but in addition to the limitations of the existing clinical data, on the

outcomes data, those two products are not the same Taxol and Abraxane, they are not the same from a pharmacological point of view both in terms of the kinetics that is achieved, the peak levels are much higher.

We don't really know what we are measuring in plasma, whether it's unbound drug, whether it's total drug, and most importantly, from my perspective is the fact that we have differential safety in terms of the neuropathy and the neutropenia. The neutropenia favors this product and the neuropathy works against it.

So, for both of those reasons, I believe that a clinical trial offers sufficient size that satisfies substantial evidence, but at the same time, compromises on the sample size and the duration.

DR. SWAIN: I am Sandra Swain. I would vote Yes, and I think we should continue with our rigorous scientific evaluation especially in the adjuvant setting in these patients that are mostly curable.

My major concern is not the efficacy. I think the efficacy is probably there, if not as good, maybe better, but probably similar, is more the safety issues with the increased neurotoxicity in these patients, as I said, who are curable and long-term effects.

DR. SIMON: I will vote Yes in the sense that I think the current data is not adequate, so I think some additional kinds of data are adequate, and I believe in randomized trial data. Exactly whether it can be done in a particularly high-risk patient population to keep the size and the time frame minimal, I think that is a direction that should be pursued.

DR. HUSSAIN: Thank you.

We have 13 Yes and 1 No. Did you want us, Dr. Pazdur, to proceed to the discussion?

DR. PAZDUR: I think what we have heard here is that people would like us to perhaps look at a high-risk population, and here again, I think the specifics of this have to be worked out with the sponsor.

That is not the purpose of this meeting obviously to come to a consensus on what the new trial should be, but we have heard from you the belief that there should be a definite randomized trial, perhaps not done in the entire adjuvant population, but perhaps in a high-risk category or perhaps in a Stage III population.

DR. HUSSAIN: With some reasonable sample size.

DR. PAZDUR: Yes. Here again, we are committed to work with the sponsor, as I said before, to come up with a trial that could be done in a realistic period of time.

DR. HUSSAIN: Are there any questions you want us to address before I adjourn?

DR. PAZDUR: If somebody else has some other ideas that they would want to express that wasn't expressed during the vote.

DR. HUSSAIN: Okay. I want to make one announcement, and that is the next ODAC meeting is going to be December 6 and 7, so please mark your calendars.

With this, we will adjourn this meeting and thank you to all.

[Whereupon, at 11:40 a.m., the Meeting was adjourned.]

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