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PARTICIPANTS

Silvana Martino, D.O., Acting Chair (A.M. Session)
Maha Hussain, M.D., Acting Chair (P.M. Session)
Johanna M. Clifford, M.S., RN, Executive Secretary

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Pamela J. Haylock, RN, Consumer Representative
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Gregory H. Reaman, M.D.
Maria Rodriguez, M.D.

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FOR COMBIDEX

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William Bradley, M.D., Ph.D.
Marion Couch, M.D., Ph.D.
Ralph D'Agostino, Ph.D.
Mark Dykewicz, M.D.
Armando Giuliano, M.D.
Dennis Ownby, M.D.
Dana Smetherman, M.D.

PATIENT REPRESENTATIVE (VOTING)

Eugene Kazmierczak - for Combidex and Prostate Cancer Endpoints

CONSULTANTS
PROSTATE CANCER ENDPOINTS
Victor DeGruttola, Sc.D.
Mario Eisenberger, M.D.
Eric Klein, M.D.
Lisa McShane, Ph.D.
Derek Raghavan, M.D., Ph.D.
Howard Sandler, M.D.
Howard Scher, M.D.

PARTICIPANTS (Continued)

FDA (A.M. Session)

Zili Li, M.D., MPH
Florence Houn, M.D.
George Mills, M.D.
Sally Loewke, M.D.

PARTICIPANTS (Continued)

FDA (P.M. Session)

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Dan Shames, M.D.
Rajeshwari Sridhara, Ph.D.
Robert Temple, M.D.
Grant Williams, M.D.

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P R O C E E D I N G S

Call to Order and Introductions

DR. MARTINO: Good morning, ladies and gentlemen. I would like to begin the meeting, if you would be so kind as to take your seats.

The purpose of this morning's meeting is to consider a new drug application, the agent Combidex from Advanced Magnetics, Incorporated, a proposed indication for intravenous administration as a Magnetic Resonance Imaging contrast agent to assist in the differentiation of metastatic and non-metastatic lymph nodes in patients with confirmed primary cancer who are at risk for lymph node metastases.

We will start the meeting by having the members of the panel introduce themselves, and I would like to begin on my left, please.

DR. LOEWKE: Sally Loewke, FDA. I am the Deputy Division Director for the Division of Medical Imaging and Radiopharmaceutical Drug Products.

DR. MILLS: Good morning. I am George

Mills, FDA. I am the Division Director for Medical Imaging.

DR. HOUN: Florence Houn, Office Director, FDA.

DR. LI: Zili Li, Medical Team Leader, FDA.

MR. KAZMIERCZAK: Eugene Kazmierczak, Patient Consultant to FDA for prostate cancer.

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

DR. BRAWLEY: Otis Brawley, Medical Oncologist and Epidemiologist, Emory University.

DR. DOROSHOW: Jim Doroshow, Division of Cancer Treatment and Diagnosis, NCI.

DR. RODRIGUEZ: Maria Rodriguez, Medical Oncologist, M.D. Anderson Cancer Center.

DR. REAMAN: Gregory Reaman, Pediatric Oncologist, Children's Hospital, Washington, D.C., and George Washington University.

DR. MARTINO: Silvana Martino, Medical Oncology, Cancer Institute Medical Group in Santa Monica.

MS. CLIFFORD: Johanna Clifford, Executive Secretary to the Oncology Drugs Advisory Committee.

DR. HUSSAIN: Maha Hussain, Medical Oncologist, University of Michigan.

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

DR. MORTIMER: Joanne Mortimer, Medical Oncologist, Moores UCSD Cancer Center.

DR. OWNBY: Dennis Ownby, Pediatric Allergist at Medical College of Georgia.

DR. D'AGOSTINO: Ralph D'Agostino, Biostatistician from Boston University.

DR. DYKEWICZ: Mark Dykewicz, Professor of Internal Medicine, Allergy and Immunology, Training Program Director, St. Louis University.

DR. GIULIANO: Armando Giuliano, Surgical Oncologist from Los Angeles.

DR. BRADLEY: Bill Bradley. I am a Neuro MRI guy. I am the Chairman of Radiology at UCSD.

DR. AMENDOLA: Marco Amendola, Professor

of Radiology, University of Miami.

DR. SMETHERMAN: Dana Smetherman, Radiologist, Section Head of Breast Imaging, Oschner Clinic.

DR. COUCH: Marion Couch, Head and Neck Surgeon from the University of North Carolina.

DR. MARTINO: If you would all turn off your mikes, and for those of you that are new to the committee, please recognize that you need to speak into the microphone, and it only works when you have pushed it and the red light is on. Once you are done with its use, please turn it off.

There is a reasonable amount of echo that I still hear in this room. Can Audiovisual do anything more to clarify our sound? Okay.

At this point, Ms. Johanna Clifford will report on the Conflict of Interests.

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.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Antonio Grillo-Lopez is participating in this meeting as an acting industry representative acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Disease Research.

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. MARTINO: Dr. Mills, if you would address the group.

Opening Remarks

DR. MILLS: Thank you, Dr. Martino.

Good morning, Committee. The sponsor of the application in this morning's session, Advanced Magnetics, requests marketing approval of Combidex for the proposed indication of assisting in the differentiation of metastatic and non-metastatic lymph nodes, in patients with confirmed primary cancer, who are at risk for lymph node metastases.

The Agency is asked to consider an indication specifically for differentiating metastatic from non-metastatic lymph nodes with little restriction on the cancer type, clinical staging, and whether the patients have been previously treated.

The Agency is in the second review cycle

for this imaging product. The first review cycle concluded with an approvable action and the sponsor was asked to conduct additional studies to address issues related to inconsistent efficacy results among the differential trials and to provide a clearer identification for the conditions of use for Combidex.

In addition, the sponsors were asked to address safety issues related to Combidex-induced hypersensitivity reactions.

In today's presentation, the sponsor will address these deficiency issues by using data that were originally submitted to the Agency, along with new information from a published study in the New England Journal of Medicine.

The Agency's presentation today will focus on whether the primary analyses that were based on 99 subjects from the U.S. studies and only 48 subjects from the European studies are adequate for marketing approval based on the sponsor's proposed indications, which reads as follows:

"Combidex is for the intravenous

administration as a contrast agent for use with MRI. Combidex can assist in the differentiation of metastatic and non-metastatic lymph nodes in patients with confirmed primary cancer who are at risk for lymph node metastases."

Today, we will be seeking comments on the issues related to the sample size and the adequacy of tumor type presentation. We will be presenting the variable efficacy results by the tumor type and the size of the lymph nodes.

We are seeking your opinion as to whether these results suggest that the variations in efficacy performance of Combidex are related to the different tumor types and to different lymph node sizes.

Today, we are seeking your advice on how to better define the conditions for use for Combidex, assuming the validity of the efficacy results, so that use of Combidex can provide benefits to patients particularly in affecting patient's treatment decisions. This point is particularly important given the risks of

hypersensitivity reactions associated with Combidex.

Lastly, we will be seeking your recommendations on what additional data are needed if current data are found to be inadequate for the marketing approval of Combidex at this time.

This concludes the Agency's introduction to the morning session.

Thank you, Dr. Martino.

DR. MARTINO: Thank you.

For those of you that are new to the committee and are consulting to the committee, the final task that we will bring to you is answers to certain questions that have been posed to the committee by the FDA. Those are in a written format and each of you should have those at your desk.

They are titled as Discussion and Questions, so please recognize that it is very specifically to answer those four questions which will be the focus of the discussion at the end of this morning's presentations.

At this point, I would like to ask Dr. Roessel from the company to introduce their speakers and proceed with their presentation.

There will be an opportunity for questions both to the sponsor, as well as to the FDA. I ask that you hold your questions until their presentations are completed.

Sponsor Presentation

Advanced Magnetics, Inc.

Combidex, Introduction and Indication

MR. ROESSEL: Good morning. Thank you, Madam Chairman, members of the Advisory Committee, FDA.

I am Mark Roessel, Vice President of Regulatory Affairs, Advanced Magnetics.

Today is an important day for us as we have been working since 1992 to bring Combidex to clinicians and cancer patients. We are pleased to be able to show you today data from controlled clinical trials demonstrating the safety and efficacy of Combidex and the great potential it has for improving imaging in cancer patients.

We have a number of distinguished consultants and speakers here today including radiologists, surgeons, oncologists, and they are available to answer any questions you may have at the end of the meeting.

I want to bring your attention to the indication. It has been read twice already. It is for a differentiation of metastatic and non-metastatic lymph nodes in cancer patients.

Here is the agenda we are going to have in our presentation and the key topics. Dr. Mukesh Harisinghani is going to show you the mechanism of action of Combidex and how it appears on MR images.

Dr. William Goeckeler from Cytogen Corporation, Vice President of Cytogen, who is our marketing partner, is going to present to you data from Phase III controlled clinical trials that were designed in cooperation with the FDA for approval of the agent.

Dr. Jerry Faich is going to review the safety data available, demonstrating that Combidex can be safely administered using dilution and

infusion.

Finally, Dr. Jelle Barentsz, a clinical investigator with Combidex, is going to review with you the clinical utility of Combidex in various cancers.

Combidex is a diagnostic tool that improves the anatomic imaging that is done every day.

Now, I would like to have Mukesh Harisinghani.

Mechanism of Action, Combidex

Appearance on MR Images

DR. HARISINGHANI: Good morning, Madam Chairman, members of the Committee, ladies and gentlemen.

What I am going to do in the next couple of minutes is to review what are the current limitations of lymph node imaging as we practice radiology today, also give an overview of how Combidex is acting and how it allows us to differentiate benign from malignant lymph node, and then also show you some examples of how it improves

sensitivity and specificity for nodal characterization.

So, the question is why do we need to image lymph nodes, and I think one needs to accurately stage primary cancer, and in doing so, it is very important to know what the nodal status is.

It is very important to know this information to appropriately treat the patients. Just to give you an example, in prostate cancer patients, if the nodes are found to be metastatic, it essentially commits the patients to non-surgical modes of therapy.

We also need to get a sense of prognosis, and that is another factor why nodal metastases are important. Again, to give you an example in bladder cancer, if the patient is node-positive, the five-year survival is way lower than if the patient is node-negative.

The risk of death also increases 20 percent with each additional node being positive.

The current lymph node staging as is

performed today involves non-invasive imaging techniques, which essentially incorporates the cross-sectional modalities like CT and MR, and the other is the invasive modes, which is essentially surgery, which are considered to be the gold standard today.

When one talks of the non-invasive cross-sectional modalities for staging lymph nodes, the predominant yardstick by which we differentiate benign from malignant lymph nodes is the size criterion, and this is what we use.

If the node is oval and less than 10 mm in size, or if it is rounded and less than 8 mm in size, we label the node as benign.

In contrast, if the node is oval and greater than 10 mm, or is rounded and greater than 8 mm, we label the node as malignant.

So, let's apply the size criterion to these two individuals. These are two different patients, both have obtained a CT scan for staging purposes.

The example on your left is an enlarged

node in the pelvis, which measures 18 mm and is rounded. No matter which size criterion you use, you would label this node as malignant.

The example on your right is a different patient, again a patient with a primary pelvic tumor. There is a small node in the pelvis, which measures 5 mm. Again, no matter which size criterion you use, you would label this node as benign.

But at surgery, it was exactly the opposite. Thus, you can see that size criterion is an inaccurate yardstick by which we categorize nodes today.

Morphology has been to a certain extent used in conjunction with size criteria occasionally, and one of the important morphologic features we rely on is presence of fatty hilum, as you are seeing here.

It is said that if the node has a central fatty hilum, that is a sign of benignity, however, we have seen from our experience that even small nodes, as the case here, with the fatty hilum in

this patient with bladder cancer, was biopsy proven to be positive and having malignant cells.

Thus, morphology, too, has its drawbacks and when used with size criterion, can be a problem.

Central necrosis is the other morphologic feature which has occasionally been said to be a very useful way to allow for diagnosing malignant nodes, but it is important to realize that when nodes become necrotic, they are enlarged beyond a cm, and by size criterion, you would still call them positive.

Well, what about surgery, which is considered to be the gold standard, and I am going to use prostate cancer as an example, but I think the underlying principle can be applied or extrapolated to other tumors, as well.

In prostate cancer, pelvic lymph node dissection accompanied by frozen section path examination is considered to be the gold standard. However, the way lymph nodes are sampled today, at the time of surgery in intermediate to high risk

prostate cancer patients, the standard pelvic lymphadenectomy is limited. This is because the surgeon only resects the low external iliac and the obturator group of lymph node.

In the recent or not too recent, in an April 2000 study published in the Journal of Urology, it was shown that if the surgeon extends the lymphadenectomy and takes out the high external iliac and the internal iliac nodes, keeping all other risk factors the same, the incidence of lymph node metastases jumps from 10 to 26 percent, so you can see that a potential of 16 percent miss rate if one just follows the standard pelvic lymphadenectomy.

So, that begs that question why don't we do that in all the cases, because there is a significant morbidity that comes with that procedure. Moreover, it is also important to realize that the frozen section analysis can also have a false negative rate of 30 to 40 percent, so all these factors show us the limitations of how even when surgery is performed and nodes are

sampled, there are some limitations.

Here is an example of a patient who had underwent radical prostatectomy, and you can see clips where the surgeon has taken out the lymph nodes, and as I said earlier, this is what standard lymphadenectomy involves, is the low external iliac group of lymph nodes.

There was a small nod posteriorly in the pelvis that was not sampled, and the patient was labeled as cured. Eight months later, the patient shows back with that node mushrooming into a full-blown metastases, and this is a good example of how surgical sampling can sometimes be limited by what the surgeon can see and samples.

Thus, there is a current need for a non-invasive technique that not only detects, but also characterizes lymph nodes with a high level of accuracy, not compromising sensitivity for specificity.

It also provides a broad anatomy coverage which means you not only look at lymph nodes right next to the primary cancer, but also can look at

lymph nodes in a broad anatomic area beyond the confines of the regional distribution.

That is where I think Combidex, or the pharmacologic name ferumoxtran-10, is an excellent contrast tool that can be utilized with MR. This is an iron oxide based nanoparticle with a central iron oxide coat and a surrounding dextran coating.

This slide shows how the contrast acts. After intravenous injection, the contrast lingers in the blood vessels for a long time, has a long blood half-life. It gradually leaks out and then is transported to the lymph nodes where it binds to the scavenger on macrophages. Thus, the mechanism of action of uptake in the normal nodes is via macrophages. So, if the node is functioning normally and has its normal complement of macrophages, the contrast would then localize to the nodes and turn the normal area of the node dark.

I would like to emphasize at this point, two points in the mechanism of action. One is the contrast is targeting the normal lymph node and

black is benign, so it is the normal part of the node that is turning dark.

If you have an area of tumor deposited in the node, then, that area of the node is devoid of normal functioning macrophages and that area would show lack of uptake and continue to stay bright.

Another important point to remember is that this mechanism of action is independent of which primary cancer affects the node, and, hence, the lack of uptake would be present no matter which tumor deposit is present within the lymph node.

This slide is just to show the technique that we use. Any conventional 1.5 MR system that exists today in the community, independent of vendor platform, can be used for imaging the MR with Combidex, and these are the sequences, again nothing fancy, just regular bread and butter sequences.

We can do post-processing, which can provide for elegant ways of communicating the information, but these are not essential for making the diagnosis.

So, let me show you an example of how the Combidex acts in real life. This is a patient who has a known pelvic malignancy. There are two lymph nodes in the groin. Both are hyper-intense or bright on the pre-contrast.

Twenty-four hours after injection of Combidex, you can see the medial node is turning homogeneously dark, and that is the node that is benign. The node to the right shows lack of uptake, and that means that it's infiltrated with cancer and, hence, it is not taking up the Combidex.

Let me show you some examples of how Combidex scanning improves sensitivity in detecting metastases in small lymph nodes.

This is a patient with prostate cancer undergoing staging. The yellow arrows point to two very small nodes next to the external iliac vein. Again, by size criterion, you would never call these nodes positive.

On the pre-Combidex scan, you can see these two nodes are hyper-intense, and 24 hours

later after Combidex, the inferior one is turning homogeneously dark. It means that that is benign. The one which is pointed by the red arrow shows lack of uptake, and that is the one which is malignant, which was proven at the time of surgery.

This is a patient with breast cancer. Again, the patient is lying prone. Here is the lung, the breast of the patient, and we are looking at the axilla. Again, there are two very small nodes in the axilla pointed by the yellow and the red arrow, measuring between 3 to 4 mm.

After giving Combidex, the superior one is turning dark as outlined by the yellow arrow, the inferior one, which is the red arrow, shows lack of update, indicating it's malignant and again proven with surgery.

So, I have shown you how Combidex improves sensitivity in different types of primary cancers. It is equally important to have enhanced specificity, which means if the node is enlarged, you need to accurately diagnose it as benign or malignant.

So, here is a patient with bladder cancer. You have an enlarged node measuring 20 mm, and this was labeled as malignant on the contrast-enhanced CT. On the pre-contrast MR, it is hyper-intense. Post-Combidex, it turns homogeneously dark indicating it's benign and was proven so on biopsy.

Another example of enhanced specificity, again a patient with prostate cancer. The two yellow arrows point to enlarged obturator nodes, again labeled malignant based on the size criterion, but post-Combidex, you can see it is turning homogeneously dark, and these turned out to be reactive enlarged nodes or reactive benign nodes in the pelvis.

As you can see, by improving the sensitivity and specificity in these patients, one can provide for improved clinical staging, and then also provide for better surgical planning and better radiation therapy and image-guided intervention planning. Some of these points will be highlighted later by my colleague, Dr. Jelle Barentsz.

Thank you

Efficacy Data from Phase III Clinical Studies

DR. GOECKELER: Good morning. I am going to review in the next few minutes the efficacy data in support of the proposed indication. The studies I will be discussing were designed to evaluate the ability of Combidex to improve the differentiation of metastatic from non-metastatic lymph nodes, particularly in the post-contrast setting.

To do this, we compare the parameters of sensitivity and specificity in both the pre- and post-contrast image sets. The study's design, which was conducted in cooperation with the FDA, provided for multiple primary tumor types and independent blinded evaluations of image sets with histopathologic confirmation of the imaging data.

I think it is worth taking just a step back to say that all the imaging data that you will be presented this morning by the sponsor involves histopathologic confirmation at the individual node level, which is a significant undertaking.

So, in reviewing the efficacy data, I will

first go over quickly the blind read procedures that were used in conducting the analysis of this data, review the data from EU and U.S. Phase III studies, talk a little bit about data from publication in the New England Journal of Medicine that investigated the agent in this application, and finally, close by looking at how this improvement in differentiation at the nodal level impacts clinical nodal staging.

So, first, the blinded read procedure, and there are a number of blinded reads that were carried out in each of the clinical studies, so I will try to explain the terminology and the sequence in which they were conducted.

All the blinded reads were carried out with the readers blinded to clinical, demographic, and pathologic information, and the cases were presented in random order.

The readers were first presented with the pre-contrast images, and based on the pre-contrast images alone, made an assessment on size based.

You will also see that in some of the

slides called an MRI-based diagnosis, and then the reader made a second assessment based solely on the pre-contrast image, which was based on the reader's skill. In that subjective evaluation, the reader was allowed to use any criteria they thought was appropriate in differentiating metastatic from non-metastatic lymph nodes.

Following those readings, the readers were presented with the post-contrast images and carried out an evaluation of the post-contrast side by side with the pre-contrast images. This is a so-called paired evaluation. The prospective primary endpoint in each of the Phase III studies was a comparison of the paired evaluation with the pre-contrast size-based evaluation at the nodal level.

Next, a period of about two weeks to eliminate a recall bias was allowed, and then the readers were presented, again in random order, with the post-contrast only images, and then made an assessment based only on the post-contrast image, which is called the post-contrast evaluation.

Post-contrast images, there were reading guidelines developed to assist the reader in evaluating the nodal post-contrast images. They were prospectively developed and finalized before the blinded read. Thus, the Phase III blind read of images is a valid assessment of nodal images across a wide range of cancers.

This is the study population in the three studies that I will be talking about - the U.S. Phase III, the EU Phase III, and the New England Journal. The number of patients dosed and the number of patients with histopathology is not always the same since eventually, not all patients go to surgery for things that happen in the intervening time between the imaging session and the treatment of the patients.

This outlines the number of lymph nodes that were evaluated in the various studies both pre- and post-contrast and a breakdown of where those lymph nodes resided by anatomic region in the various cancers.

So, right into the Phase III study, in the

EU Phase III study, what we see is that in the pre-contrast evaluations, both the size and the subjective base, we see a high pre-contrast sensitivity and a low pre-contrast specificity, whereas, in the post-contrast evaluation, the paired evaluation, what we see is sensitivity remains high at 96 percent, but specificity is significantly improved, and the improvement in specificity was statistically significant over both of the pre-contrast reads and for both of the blinded readers.

We look at the data from the U.S. Phase III study. It's a little bit different situation. In the pre-contrast size-based analysis, in the pre-contrast analysis, sensitivity was low and specificity was high, so sort of just the opposite of what was seen in the EU study.

In the subjective evaluation, we see that the subjective reader's assessment resulted in a very high sensitivity, but the tradeoff for that increase in sensitivity was a large decrease in specificity.

So, the pre-contrast reads had either high sensitivity or high specificity, but not both. In the post-contrast reads, you will see that sensitivity was high and specificity was high, so we had a combination of high sensitivity and high specificity.

You will also note that in the post-only read, in which the only image that was available was the post-contrast image, resulted in the highest level of imaging performance and the greatest level of consistency.

If we take a look for just a minute at this discrepancy between the two pre-contrast reads, where one had high sensitivity and low specificity, and the other was the opposite, if we look at the false diagnoses that occurred in these various blinded readings, and we look at false diagnoses as a percentage of the total, we see that the percentage of false diagnoses for both of the pre-contrast reads is relatively the same.

What we see is that in the subjective readers' diagnosis with the readers subjectively

overreading to try to account for the known low sensitivity of the size-based analysis, we see a very large percentage of false positive reads that occur in the subjective readings, whereas, in the post-contrast reads, we see a decreased percentage of false reads with the lowest and most consistent data again in the post-only read.

This is the data broken out by body region, and you can see that in the head and neck and breast, we saw large increases in sensitivity when we compare the pre- to the post-contrast read, maintaining specificity which overall resulted in the increase in accuracy.

In the pelvis and abdomen, we had more moderate levels of increase in both sensitivity and specificity, the net effect of which is that the increase in accuracy in the pelvis and abdomen is virtually identical to what one sees in both the head and neck and the breast.

One region that was a little bit different was in the lung. In the lung, we see more moderate, small increases in both sensitivity and

specificity, and we believe this has to do with limitations of anatomic imaging in this particular body region, and not differential uptake or performance of the contrast agent.

So, turning now to the data published in the New England Journal of Medicine, and I think this data is important supplemental data that can help us understand better some of the differences that were seen particularly in the pre-contrast reads in the Phase III studies and also can help us learn a little bit more about the performance of the agent in different size nodes.

So, this is a study carried out in prostate cancer patients at two centers, one in the U.S., one in the EU, 40 patients from each site. There was a centralized independent blinded read with histopathologic confirmation of data.

So, to address some of the issues that I just mentioned, I am going to go through the data in a little bit of a sequential order.

First, with regard to the issue of the discrepancies in the pre-contrast evaluations and

also to look at the issue of the effect of nodal size on the performance of the contrast agent, what you see is as you move across these three studies, the distribution of nodes categorized as either greater than or less than 10 mm, and that is an appropriate cut point because as Dr. Harisinghani said earlier, that is the point at which we differentiate a malignant from a non-malignant node.

We see that as we move from the EU to the U.S. to the New England Journal study, the proportion of large nodes are greater than 10 mm in the yellow, goes from about three-quarters to about a third to only 7 percent in the New England Journal study.

We see in the pre-contrast size-based sensitivities and specificities, we see that the sensitivities and specificities largely track with the nodal size. That is, in studies where there was a high proportion of large nodes, we see a high sensitivity in the pre-contrast evaluation in the green bars, which decreases as the proportion of

large nodes in the study decreases.

Conversely, as in the purple bars, we see that as the percentage of small nodes increases, then, the specificity increases also.

So, finally, in the post-contrast data, what we see is that we see a lack of dependence of the performance of the agent on the size of distribution of the nodes in the study. We have high sensitivity and specificity regardless of the distribution of the lymph node sizes that were in those studies.

Finally, just a word about clinical nodal staging in the U.S. Phase III study, we looked at clinical nodal staging where we could collapse the nodal stage in its simplest form to where patients were either node positive, node negative, or indeterminate.

What we see here is a comparison of the clinical nodal stage that was assigned based on the images compared to the eventual pathologic stage, and we can see as we go from the pre- to the post-paired to the post, the percent where the

agreement was correct increases, the percent where it's incorrect decreases, and the percentage that could not be staged also decreases.

So, to sum up, there are two prospective Phase III studies. The pre-contrast evaluations in these studies show a characteristic tradeoff of sensitivity for specificity. Post-contrast evaluations show high sensitivity and high specificity, which results in an overall improvement in accuracy.

The improved lymph node differentiation improved clinical staging. The supporting data from the New England Journal publication showed high sensitivity and specificity in a population of largely small lymph nodes.

Finally, these data collectively demonstrate the efficacy of Combidex in differentiating metastatic from non-metastatic lymph nodes.

Thank you. Now, Dr. Faich will review the safety data.

Safety Data from Clinical Trial

DR. FAICH: I am Jerry Faich. Good morning, members of the panel, Chairman, and FDA.

What I would like to do rather briefly is review the amount of exposure data that has been obtained for Combidex, discuss and show you the pattern of adverse events that have occurred, make a few comparisons with other agents, and then discuss the proposed risk management plan for the product.

In total, 2,061 subjects have been dosed with Combidex. Of these, and I would like to emphasize this and explain it, 131 received bolus injection. This was in the process of developing or exploring the utility of the product for liver scanning, which required a bolus injection. That indication and mode of administration has been dropped.

The remaining patients, the remaining 1,930 patients were dosed with dilution and infusion either in 50 ml or 100 ml saline, and within those, there were 1,566 cases at all doses who got the 100 ml dilution.

For the proposed indication and mode of distribution, there were 1,236 patients in the NDA receiving 2.6 mg of iron/per kg at the 100 ml dilution over 30 minutes.

This shows you on the left-hand side the rate of adverse events in the bolus injection 30 percent, in the middle 17 percent for 50 ml dilution, and 14 percent on the right-hand side for 100 ml dilution showing a clear dose-response relationship in terms of adverse events, and this is indeed why the 100 ml dilution has been focused on.

It needs to be said that during the bolus injection studies, there was one anaphylactic death that occurred immediately. That and the need to use bolus injection for liver scanning is what led to dropping the pursuit of that indication.

This shows you in the 1,236 patients the pattern and rates of adverse events, you can see going from vasodilation at 3.4 percent, rash, back pain, pruritus, urticaria, et cetera, overall totaling these 15.8 percent.

I would simply like to emphasize that nearly all of these were mild, transient, and self-limited.

Within the 1,236 core patients, 5.6 percent had adverse events from that prior list that could be called hypersensitivity events. Mainly these were vasodilation. It included 24 patients, however, who had more than one symptom from that list.

Only 4 of the 1,236 patients, or 3 per 1,000, had a serious adverse event. The serious adverse event rate is no greater than that found in labeling for nonionic iodinated contrast media, which ranges from 0.6 to 1.5 percent, and I will show you that in a moment.

There were no life-threatening anaphylactic/anaphylactoid reactions at the proposed dose and method of administration.

In terms of immediate adverse events, immediate hypersensitivity adverse events can, of course, be controlled in large part by stopping the infusion. The most common reaction, as I noted,

was flushing.

Thirty-six patients had infusion stopped and restarted, that is, these patients were rechallenged. Only two of them could not tolerate the rechallenge and were discontinued. The remaining 36 went on to complete their procedure.

Put a slightly different way, 94 percent of all immediate hypersensitivity reactions occurred within the first 5 minutes after dosing. Most hypersensitivity reactions, as I indicated, were mild to moderate in intensity.

At the proposed dose and method of administration, out of the 4 serious AEs, 2 were classified as immediate hypersensitivity reactions using the FDA definition. That translates to a rate of 1.6 per 1,000.

In terms of anaphylactoid reactions, again using an FDA definition of affecting two body systems, there were 12 such patients at the proposed dose and method of administration. Two of those were considered serious.

Four of the 12 were in the group that had

infusion stopped and then were rechallenged without subsequent problems. The majority of these 12 had dyspnea and flushing. There were no serious hypotension or respiratory compromise seen in those 12 patients.

I don't mean to make much of this, but I do show it, and it is always hazardous, and one has to interpret data carefully when you compare one set of data from one set of studies and labels to another, but what I would like to do here is call your attention to the Combidex data across the top.

The overall AE rate was 15.8 percent, the serious AE rate was 3 per 1,000. That is those 4 cases I mentioned. If you look down in the right-hand column just at serious AEs and compare it to other iodinated contrast agents, both from data in their labels and published studies, you will see for Ultravist, that serious AE rate is 1.1 percent.

For comparators in studies done with Ultravist, it was 0.6 percent, for Oxilan it was 1.5 percent, and for comparators to Oxilan and

studies done with it were 1.1 percent. So, this is a basis or my basis for concluding there is not evidence that there is increased risk of serious adverse events comparing this drug to commonly used iodinated contrast agents.

There is not much in the literature about anaphylaxis in contrast agents. Here are 2 recent studies that have been published. This is Neugut in the Archives of Internal Medicine. His published anaphylaxis rate done from his own studies and across the literature was 2 per 1,000 to 10 per 1,000 or 0.22 to 1 percent. He noted that it might be lower and most people are taking a rate of about half that for low osmolality contrast agents.

David Kaufman, at the Center for Epidemiology in Boston, published this paper in 2003, and for contrast agents, this was an international study of anaphylaxis, the observed rate was 7 per 10,000. For nonionics, again, as I said, 50 percent of that, about 3.5 percent, and there was a range as you see here.

Combidex falls within or at the lower end within that range of values.

In terms of a risk management plan for this product, it is largely in keeping with existing guidelines and calls for physician education, emphasizing the need for dilution and slow infusion obviously as a means to be able to intervene if a reaction is occurring. The labeling will be consistent with that, and the proposal is to conduct targeted surveillance to gather further data to reinforce the safety data that I have shown you.

To summarize, then, there has been considerable clinical exposure in the development program. Hypersensitivity is relatively infrequent and comparable to that of other contrast agents, and the risk management program that I just described is in accordance with existing guidelines. Thank you.

Dr. Barentsz, please.

Clinical Utility of Combidex in Various Centers

DR. BARENTSZ: Madam Chairman, members of

the Committee, members of the FDA, I am an oncologic radiologist and I have been using Combidex MRI in more than 500 patients, and I am in frequent contact with investigators in both the U.S. and in Europe.

From the previous data, you have clearly shown that this contrast agent works. A black lymph node is normal, and a white lymph node is abnormal. That is despite the tumors type.

Nonetheless, evaluating its clinical utility is a lot more difficult, and for that you need personal experience, as well as post-Phase III studies. Based on these two, I am going to try to show you the clinical utility and some cancer types.

The reviewed publications were all in top ranking journals. It was blinded post-contrast image evaluation with gold standard histopathology, and all those papers described a potential impact on treatment planning.

The areas being defined where Combidex MRI provides a significant clinical benefit were

prostate, bladder, head and neck, and breast, and I want to address those issues with you in the next 10 minutes.

As you can see, data were collected from almost 200 patients and almost 2,000 lymph nodes. These are the data on sensitivity and specificity and accuracy.

You can see that the data are highly consistent, showing a high sensitivity, specificity, and accuracy for all the cancers.

Now, let's start with the clinical utility in prostate cancer. First of all, you have to define the current strategies. Current imaging has an insufficient sensitivity for lymph node staging, and therefore, urologists are performing an invasive operative surgical lymph node sampling to detect the lymph nodes.

These techniques have limitations, only a limited area sampled, and therefore, up to 31 percent of the positive lymph nodes are outside of the surgical area, which have been shown by some data recently published in the urology journals.

Furthermore, surgical sampling has a complication rate reported to be 22 percent for the open dissection and 5 percent for laparoscopic dissection, including lymphocele, lymphedema, deep venous thrombosis, pulmonary embolism, nerve damage, and blood loss.

Because of the limitations of current imaging technique and current staging techniques for the lymph node dissection, these urologists are advocating at this moment now an extended lymph node dissection. They state that they will detect those lymph nodes, however, this significantly increases morbidity. The question is are the less invasive way techniques to solve this problem.

As you can see, using the post-contrast studies of Combidex, there is a dramatic decrease of the number of false positives, as well as the number of false negatives, but what is even more important is that in our study in the New England Journal of Medicine, in 6 percent of all the patients, we found a small non-enlarged lymph node which we could biopsy, and in all those patients,

we could confirm the diagnosis by image-guided biopsy, and these patients did not undergo any surgical dissection.

Furthermore, in 11 percent, we found lymph nodes which were outside of the surgical field, so they will be missed with regular surgery.

All these findings were confirmed by the surgery because before the operation, we told the urologists where the lymph node was, and they could then find them.

I would like to show you two representative cases. Here, you see a white lymph node, metastatic, of only 7 mm in size. It is very close to the internal iliac artery, which is outside of the normal surgical field. In this lymph node, we performed an image-guided biopsy which was positive, and in this way a correct diagnosis was being evaluated in a less invasive manner, and this avoided inappropriate treatment. This patient had, instead of a prostatectomy, an androgen ablation.

In another patient, you see a lymph node

over there with a tiny white structure. You can see it over there. This was also a lymph node outside of the surgical field. We told our urologist where this lymph node was located. It was found and it was confirmed histopathologically that this lymph node had a 1-mm metastasis.

What about bladder cancer? It is actually the same story. In 24 percent of positive lymph nodes, there are positive lymph nodes in 24 percent despite negative pre-operative imaging techniques.

The presence of lymph nodes radically changes the treatment option especially if there is N2 and 3 node, or if there are more than 4 nodes, so finding these lymph nodes also here is very important.

If you perform an extended lymph node dissection, you detect more lymph node, it will increase survival for minimal disease, however, also in this extended lymph node dissections, not all lymph nodes have been sampled. Furthermore, this increases morbidity.

These are the data in 172 lymph nodes in

58 patients from a Radiology paper, and it has been shown that in normal-sized lymph nodes, 10 out of 12 were detected using Combidex MRI, and this information was crucial for the surgeon to find these lymph nodes, and they were removed.

Most important areas, also head and neck. The survival rates depends on whether the tumor has metastasis in lymph nodes or not. Therefore, the status of cervical lymph nodes is vital for the choice of therapy.

Twenty-five percent of positive lymph nodes are found despite negative preoperative imaging techniques like contrast CT or ultrasound-guided biopsy. Why? Because these lymph nodes are below normal size criteria. They are only 5 to 10 mm in size.

Because of the fact that these lymph nodes do not show up with imaging, head and neck surgeons perform commonly a radical neck dissection, which causes a very severe cosmetic deformity and has a very high complication rate, in literature reported up to 54 percent.

The data from Mack, et al. in Radiology show a very high sensitivity and negative predictive value, and furthermore, what is more important, if you look on a patient level, they were able to make an accurate diagnosis in 26 out of 27 patients, and what is the most important thing is that this information would have resulted in reduced extent of surgery in 26 percent of these patients, so avoiding an aggressive neck dissection.

One representative image. This was a patient with, on the CT scan, an enlarged 12 mm lymph nodes, however, on the post-Combidex MRI, you see the lymph nodes are black. This was the 12 mm one, this was the 10 mm one, and they were normal. In this patient, a neck dissection could have been avoided.

Finally, breast cancer. The commonly used staging procedure at this moment is the sentinel lymph node staging, which has false negative numbers of 3 to 10 percent, and is an invasive technique, but what is even more important is that

recent data have shown that the sentinel lymph node is the only positive lymph node in 61 percent in patients with positive lymph nodes.

Nonetheless, these patients all undergo an axillary lymph node dissection, and this has a high rate of clinically significant complications.

A technique with a high negative predictive value performed in an adjunct to the sentinel lymph node procedure in patients with one positive sentinel lymph node may reduce the number of axillary lymph node dissections.

These are the published data in almost 300 patients by Michel in Switzerland, and you can see that this technique has a high negative predictive value.

I would like to show you one representative case from our institution. This is a very, very tiny primary tumor, and this was the positive sample on lymph nodes. This lymph node is white on Combidex, so that means metastatic, and you can see that the second and third station lymph nodes, that they are black, so in this patient, all

the other lymph nodes were black, which in this case was confirmed by histopathology.

Now, to the final conclusion. I have tried to show you some areas of clinical utility of this contrast agent, and as soon as we get more experience, there will be a lot more areas.

To summarize, the current techniques to detect positive lymph nodes in prostate, bladder, head and neck, and breast cancer have significant limitations.

Combidex MRI shows high sensitivity and specificity not only on the nodal basis, but also on the patient-to-patient basis, which for a clinician is even more important.

Therefore, Combidex MRI may reduce the extent of surgery and morbidity, and finally, Combidex MRI identifies additional positive lymph nodes for biopsy or image-guided extended lymph node dissection in this way improving the staging of the surgeon.

Thank you.

MR. ROESSEL: Thank you. That concludes

our presentation.

Our clinical data and the clinicians I think have shown you that Combidex is an important diagnostic imaging tool that improves the current practice.

Thank you. We are available for any questions you have.

DR. MARTINO: Thank you.

At this time, I am going to ask Dr. Li to present his view of this data, and once that is done, we then will take questions for both the sponsor and the FDA.

FDA Presentation

Efficacy and Safety of Combidex (NDA 21-115)

DR. LI: Dr. Martino, members of panel, ladies and gentlemen, good morning. My name is Zili Li. I am a medical team leader with the Division of Medical Imaging and Radiopharmaceutical Drug Products at FDA. I am a board-certified physician in preventive medicine with special training in epidemiology.

Today, I would like to share with you our

review of findings of NDA Application 21-115 Combidex.

I would like to start off by noting that this presentation represents a collaborative effort by a group of highly dedicated reviewers at FDA whose names are on this list.

Combidex is an MR contrast agent. The proposed clinical dose is 2.6 milligram iron per kilo of body weight.

Of three methods of administration which has been used in the clinical development program, the sponsor select the dilution in 100 cc with the slow infusion over 30 minutes of a standard measure of administration.

The other two methods, particularly the direct injection, is no longer being proposed.

This slide summarized the indication that had been proposed by the sponsor--I will go over one more time--that Combidex can assist in the differentiation of metastatic and non-metastatic lymph nodes in patients with confirmed primary cancer who are at risk for lymph node metastases.

I would like to draw your attention to the fact that this is a broad indication. If granted, this agent can be used for almost all cancers regardless of type, size, clinical stage, whether patient has been previously treated with drug, biologic, radiation, or surgery.

One objective of today's presentation is to show you why the Agency has concerns for such a wide or broad indication given the level of efficacy and safety observed from clinical trials.

To support this indication, the sponsor submit one U.S. and three European Phase III studies. In addition, sponsor also ask Agency to consider data from a published article in the New England Journal of Medicine.

For the safety, the sponsor submitted a safety data adverse event profile in particular from approximately 2,000 individuals who received Combidex from multiple clinical studies.

I would like to make a remark on this New England Journal of Medicine article. This study is pooled analysis from two ongoing clinical studies.

One is U.S. IND study, is under sponsor's IND. The other study is non-IND study and in Europe.

The clinical investigators themselves took initiative to combine 40 cancer patients from each original study to form the basis for this New England Journal of Medicine study. At this time, however, it is unclear to us how those 80 patients were selected, and more important, after repeat requests, the sponsor is not able to provide us the original source document which included pre-defined statistical plan, blind reader evaluation manual, and original copy of blind readers' evaluation of the medical imaging.

For that reason, the Agency cannot conclude this study was conducted in compliance with the Federal regulations pertaining new drug application. For that reason, we are not able to consider this study as adequate and well-controlled study.

However, the Agency do agree that the cases present in this article may demonstrate some potential the benefit of the use of Combidex in a

clinical setting.

I also would like to draw your attention, say a few words about this U.S. IND study. We just got update from sponsor yesterday. This study is closed at this time. Roughly, they have 220 patients enrolled including 91 prostate cancer and 34 bladder cancer patients.

Although the original protocol require all the pathology confirmation and MR imaging for all the patients, at this time it is not clear to us how many patients for this study will have both information available for a meaningful analysis for efficacy if such analysis is needed.

Now, I would like to first highlight the differences between sponsor and the Agency's final conclusion regarding efficacy and for safety.

As far as for the efficacy, the sponsor believes the non-contrast MR agent only offer high sensitivity or high specificity, but not both. The advantage of this Combidex is its ability to offer both high sensitivity and specificity consistently regardless type of cancer or size of the lymph

node.

At this time, the Agency is not able to draw such a conclusion because of the generalizability and validity issues we are going to show you in the later presentation, and also in the later presentation, we are going to show some preliminary evidence which may suggest the performance of Combidex may vary by size or type of cancer.

For the safety, sponsor acknowledge that Combidex is associated with hypersensitivity reaction, however, their emphasis is that no death or life-threatening AEs are associated with the proposed clinical method of administration. That is the dilution with the slow infusion.

Also, I just noticed in the sponsor's presentation is new to us that they make a claim that this agent's safety profile is equivalent to the iodinated contrast agent. I believe in your briefing document, they also made a claim that serious adverse event with the Combidex is only one-third of that iodinated contrast agent.

Our position is that dilution and slow infusion are not entirely free, and also we disagree that the Combidex, the safety profile resemble that of iodinated contrast agent.

This slide highlights the issues we are going to bring to the panel today. For the efficacy, we are going to talk about sample size. We are going to talk about representation of different tumor types in the clinical study.

We are also going to talk about impact of study inclusion/exclusion criteria. Later, the last one, we are going to talk about develop use of Combidex imaging guidance, which was the major issue in our briefing documentation to you.

For safety, we are going to talk about the hypersensitivity reaction. We are also going to make a comparison with iodinated contrast agent.

Then, we are going to follow up with the discussion of risk-benefit ratio, including the sponsor's proposed risk management plan and our emphasis on the need to understand, to define the conditions of use for this product.

From the sponsor's presentation, it was stated that total 152 U.S. patients and 181 patients from a European study received Combidex injection, however, what was not apparent on their slide was the number of patients who were actually included in the primary analysis. What we are showing you is, because there are two different blind readers, so they may see the different people different, so the number may vary slightly.

For the U.S. study, there is only 64 percent of original total population were actually involved in the final analysis. For the European studies, the number varies from zero, 16 percent, roughly 20 percent to 41 percent. It only represent a small proportion of the patients who originally received the Combidex.

I need to make a clarification for the study with zero participation. This is a breast cancer study. You probably read our briefing document. The original statistical plan for the European study is on the patient basis. It is totally different from what they did here. So, for

that reason, the individual nodal level analysis was never performed, so those people cannot include in their primary analysis and consistent with U.S. statistical plan.

The small number of patients or small proportion of patients included in the primary analysis create two dilemmas for us. The first, we need to understand whether the estimate we got from this population is applicable to entire population.

The second one is because of the small number of patients, we want to ensure that the patients included in the analysis more represent the cancer patient distribution in the United States.

This is the second issue we would like to bring to your attention.

Based on the statistic provided by American Cancer Society, it is estimated this year, 2005, there is going to be 1.4 million new cancer diagnosed. The left two column showed you the rank of the top 10 cancers and also showed their percentage distribution in the United States. I

need to mention that lymphoma or leukemia are not included in this table.

On the right two columns show the number of patients and their distribution for each type of cancer included in the primary analysis. I would like to bring your attention to the fact they have two readers. In this slide, we pick the highest number in this table.

You probably noticed that the majority of patients come from head and neck, which is ranked roughly number 6 in the frequency distribution, and also you probably noticed that prostate cancer being the number one in the United States. There is only 5 patients from the United States and 5 patients from Europe was included in the primary analysis, and the highest number each category is only in here is 37.

Also, I need to remind you that for European study, the sponsor showed you the majority nodes are larger than 10 mm. Actually, in reality, all 37 patients have a node larger than 10 mm, so there is no nodes like the 10 mm for the European

study for this population, particularly this head and neck what I referred to.

So, you probably will ask why that so many patients are not included in the primary analysis. I would like to bring your attention to the fact the primary analysis was conduct at the nodal level, so the target lymph nodes, which should be included in the analysis, is represented here, the large circle here, is all the lymph nodes visualized by site investigators.

When patient enrolled, when they take MR, site investigator looked at the MR to circle the node they see on those MR images. That should form the basis for primary analysis. However, not all the nodes was able to match with pathology, so you drop some nodes right over there.

Then, when you present the same images, the unmarked images to blinded reader, the blinded reader may not pick up the same nodes the original investigator picked in the first place, so you drop some nodes over there.

Then, for the comparison purpose, because

they want to compare the post-images with the pre-images, you can only do analysis on the nodes identified on both end, so for that reason, you have a few nodes drop again, so by the end, the nodes included in the analysis is much smaller than the nodes originally seen by site investigator initially.

This table actually show you the deposition of how the nodes got lost with each process. In the U.S. study, this is the number of patients. The first row showed you number of nodes originally visualized by the site investigator, which should form the basis for primary analysis - 371, 834, 333, and 234.

This row showed you what percentage of those nodes have matched pathology, and this row, the final one, showed you what number, how many nodes were actually included in the primary analysis. You can see it is roughly from 3 percent, 6 percent, to 45 percent of nodes was originally seen is included in the primary analysis.

The fundamental assumption for this clinical development program is that the performance of Combidex should be independent from the type of cancer and the size of lymph nodes. That was why originally that was allowed for different cancer patients included in the one study.

However, if you look at this performance of Combidex, by different type of cancer, you will see, first, this is the sensitivity slide. You will see in the U.S. trial, the variation from 76 to 100 depending on the site of primary cancer, and the 95 percent of the lower boundary could go as low as 55 percent.

Only if you are willing to accept assumption that Combidex performance is independent of sites, you get 83 percent performance with the lower boundary 73. That is exactly the reason why the Agency was so worried about small lymph nodes, small size, because from this table we really don't know whether it's a variation because of the random event, or if it truly reflects the different

performance of Combidex among the different type of cancers.

This is the same table for the specificity, which again challenge assumption whether the Combidex, the performance should be considered or accepted independent from the type of cancers.

You notice depending on the different sites, the specificity vary from 44 to 91, and with the lower bound, can go as low as 21 percent. The significance of the two slides is that with dose variation we will have a very hard time to understand what is appropriate performance characteristic of this Combidex-enhanced MR contrast agent, and if indeed the performance are different, if this drug is approved for all the cancers, this information may be misused by the clinician to make their clinical judgment.

The next issue is about study inclusion/exclusion criteria. I will go very fast. Basically, for this study, the people who received treatment, chemotherapy or radiation therapy in the

past 6 months was excluded.

Actually, in reality, when you look at the people included in the primary analysis, I don't think any of them had any prior treatment, so mainly this database, we believe, if valid, only applied to people who are newly diagnosed patients.

This is issue about development of a clinical MR imaging guidance. Why is this imaging guidance so important? It is because for the radiation to use this contrast agent, you need to have a standard way to interpret imaging. So, we work with sponsor to ask them to come with the guidance.

So, this actually, the clinical trial is actually to validate the guidance for this validity and usefulness, however, originally, from the NDA submission, it appeared to suggest this guidance was developed and validated from the same database. That is the U.S. database. That was a big concern for us because basically, if that is true, that destroyed independence of this guidance themself.

Later on when we spoke to sponsor, they

provided us a revised statement. Basically, the guidance was developed by use of Phase II images, it is not Phase III.

Sponsor's consultant, when she developed this guidance, she did look at the 16 cases from Phase III trials, however, no pathology was provided, and also, there was a statement that there is no more changes for the guidance after review of Phase III data.

To support their statement, sponsor did submit original soft document to FDA for our verification. We also had extensive discussion with their consultant to recall what happening on that day for the development of a Combidex imaging guidance.

All we conclude at this time is that, first, we do not have definitive evidence to absolutely exclude the probability that Phase III data has no impact in this guidance development, however, the evidence provided by the sponsor is consistent with this revised statement, therefore, at this time, we decided not to pursue this issue

any further unless there is new evidence emerge.

The second issue we are having, which I will present was included in our briefing document, is in the European study, this guidance, the core instrument actually was not used by the blinded reader. The blinded reader was using a different guidance to make their diagnosis.

At this time, the sponsor is not able to provide any documentation for us to understand which method or who actually do the translation from this guidance and to this one. Actually, the question we are having for the committee, especially for people expert in MR imaging, is whether the similarity or correlation between these two guidance is so great, the Agency should not worry about who did it and with all this documentation.

Now, I would like to switch to the safety side of Combidex evaluation. I will focus my presentation in Combidex-induced hypersensitivity reaction.

There is one case hypersensitivity-related

death in a clinical development program. This is a 70-year-old male with history of allergy to contrast, who received undiluted direct injection and developed hypersensitivity reaction immediately after injection and become unresponsive.

At the clinical site, however, there were no appropriate personnel or emergency response available, so they have to call 911. When the EMT arrived, they delivered CPR and epinephrine. When the patient get to the hospital, patient was pronounced dead approximately 35 minutes after this injection. An autopsy revealed no MI or PE, and they conclude this is a Combidex-related anaphylactic shock.

I would like to make two points here. This injection is no longer being used. The second one, we are really concerned about the lack of appropriate personnel for emergency situations especially if this drug is found to be valid, safe, effective, there is many free-standing clinical imaging centers around the country, so we need to have a way to ensure this drug to be used

appropriately. That is with assumption that if this study is valid and the drug is safe.

This table shows the distribution of the safety database or number of patients by administration and by the dose. There are a total of 2,061 patients exposed to Combidex, 1,236 patients received proposed clinical dose, 131 patients received bolus injection. Those three groups will form the comparison for our next few slides.

This slide shows the rate and severe hypersensitivity reactions by the three different subgroups I just mentioned to you. For the clinical proposed dose, the rate of hypersensitivity reaction is 5.3. For direct injection, it is 6.1.

I would like to let you know that in your briefing document, this number is slightly higher because we just discovered some computer error, so made correction on this slide.

People may define the severity differently, so we use few indicators to give you a

range of severity, so you can pick which one is appropriate for you. The first one is death. The second one is serious events, which was the event that meet the regulatory definition for serious adverse event.

The next one is hypersensitivity involve at least two body systems. The next one is the patient was treated with antihistamine. The last one is the patient treated with steroid. Most of them are IV steroid.

If you look at this population, there is no deaths. There is two cases the sponsor point to you meet the definition of serious event. There is 13 cases that involve two body systems, 27, or 2.4 percent, of people treated with antihistamine, and 1.5 percent of people need IV steroids.

This slide outline the presenting symptoms of hypersensitivity reactions. We work extensively with our internal expert at FDA. We define hypersensitivity reaction with the following three groups of symptoms.

First, is skin reaction. The second group

with the respiratory difficulty with cardiovascular symptoms together. The third one with the facial, laryngeal, and general edema. This table show the distribution of the patient presentation.

You will notice the majority of patients present with skin symptoms, however, this slide does show that direct injection, they may associate with a high percentage of people with more severe symptoms.

This is a slide I would like to bring to your attention with a comparison with iodinated contrast agent. The sponsor told you that there were 4 cases serious AE happened in the clinical program. That was an incorrect statement. In reality, there was 29 serious events happened in the clinical program.

The reason for include there, because the 25 cases, the Agency do not consider is drug related, therefore, we didn't include it in our analysis.

In the comparator, iodinated contrast agents in their Table 9 safety presentation, they

are including all SAEs regardless whether drug related, so that is we believe incorrect comparison. So, that is why the number of events in Combidex group is smaller than the iodinated group.

This table, we focus on the hypersensitivity reaction between Combidex and the iodinated contrast agent. If you read the labels, three labels which have clinical data for iodinated contrast agents, totaled together there are 4,545 patients received iodinated contrast agent. There is no death happening. For Combidex, there is 1 death of all the people receive Combidex. There is zero out of 1,000 who has clinical dose.

For the serious AE, which is associated with the Combidex, this is zero over here, and you have 6 cases out of 2,000 for all doses, you have 2 cases for the clinical proposed dose.

Also, the last one, the column, we show the percent distribution of those symptoms suggests hypersensitivity reaction, you can see the rate is quite different, the relative risk is quite

different. We do not want to draw definite conclusion over here because we understand the population are different, but at least this table do not support this two rate are comparable.

When you talk about whether the drug is appropriate for populations, you basically talk about the risk-benefit ratios. From the sponsor's presentation, they believe the best way to manage to get a best ratio is to focus on the risks. I will show you their risk management slides later.

From our end, we believe from the safety data we have at this time, this drug is definitely associated with hypersensitivity reaction. Although we have not observed serious event, more serious event including death in the proposed clinical dose, our level of assurance is limited by the number of patients involved in that group of patients who received the clinical dose.

At this time, we are only able to say that the death-related hypersensitivity reaction probably will now be higher than 1 out of 400 or 500 people based on data. Anything beyond that,

that is purely speculation without any data.

Sponsor present to you their risk management program. I rearranged our slides. Basically, they say if we provided dilution and slow infusion, and educate physicians to the labeling and to the targeting academic center, they should be able to adequately address the safety issue.

We believe this is item we need to discuss to implement, and also we believe that with uncertainty with those severe events with this Combidex administration, when you focus on the issues, enhance the benefit of this drug to the appropriate population.

We need to better understand actually the performance of Combidex by different type of tumor and the nodal size, because we have preliminary evidence those performance may vary. Also, we need to define appropriate patient population or condition for use, that the use of Combidex, the benefit will outweigh the risk, potential risk.

This is a table to support our preliminary

conclusion that performance of Combidex may vary by type, by size of nodes, in addition of the type of cancer. This analysis actually was conducted by sponsor. We didn't make any modification to their slides. We just presented their slides, their result to you.

On the top is for the nodes less than 10 mm, the bottom row is for nodes larger than 10 mm. You can see for the nodes less than 10 mm, the sensitivity from their clinical database is between 67, 66 percent, and the specificity is 80 to 78 percent.

For the nodes larger than 10, the sensitivity is 93, 98 for different readers, and 56 and 71. This, I would remind you, this is just a point estimator. We have not put 95 percent lower boundary yet.

If we put in the boundary, this number could even be lower. We also don't know whether there is interaction between size and type of tumor because so small nodes that was included in the primary analysis would not allow us to do a further

analysis.

This table showed you the prevalence of nodes being positive by size of lymph nodes. Why this information is important is because the sponsor showed you the positive predictive value and the negative predictive value in their presentation.

To better understand that positive and negative predictive value, you not only need to understand the performance, that is, sensitivity and specificity of agent, you also need to know the prior probability that the prevalence of this node being positive before you give a drug.

This data collected from their studies, and for nodes less than 10, because we don't have the MR imaging measurement, so we have to use the pathology measurement as a surrogate over here. For nodes less than 10, the prevalence range from 10 to 21 percent, which means if you see nodes less than 10 mm, the probability that the nodes be cancer-positive range from 10 to 20 percent from this data.

If the nodes are more than 10 mm, then, the probability from 34 to 60 percent depending on different study. We still don't know why there is variations.

Also, you probably reviewed the New England Journal of Medicine. From their study, the percentage is even higher. They got 75 percent of people for the nodes larger than 10 has a cancer.

So, how are we going to put all this information together to understand or to help us to understand the value of Combidex to help physicians in their patient care decisionmaking, or for any other benefit that they believe is good for patients?

I will present to you the predictive values of a positive or negative Combidex test. I will go over slowly with you. For the lymph nodes less than 10 mm, the sensitivity is 68, the specificity is 80. We make this assumption. This has not been demonstrated by data yet, because the lymph nodes, the number are too small, but we assume if this is what we observed.

The prevalence tell you what is the probability the nodes is cancer, whether they are cancer-positive nodes before you give Combidex. The positive predictive value really tell you after you give Combidex, and if you get a positive result, what is the probability that node is metastatic at that time.

The negative predictive value tell you if you gave Combidex, and the result is negative, what is the probability that node is negative.

We look at different scenarios. If the prevalence is 1, based on data or based on your suspicion, the clinical knowledge, if you are thinking the node, the probability of metastasis is only 1 percent, based on this performance, even Combidex is positive, the probability that nodes being positive is only 3 percent, so the people should make their own judgment this kind of improvement where they have clinical implication or values to help you to make decision to the patient care.

When the prevalence get into 10, 25

percent, you see big changes here in the probability, and this probably will getting higher if sensitivity and specificity get improved, which means that after you get a Combidex test, these nodes more likely become cancer. You may go ahead to biopsy that one to confirm your suspicion.

However, the positive predictive value is not that high enough, so we believe with this probability or likelihood, you will never make final diagnosis based on the Combidex positive result only, so most likely you will go to biopsy to confirm it.

So, we do believe for nodes less than 10, there might be potential values for Combidex if performance is constantly demonstrated to help physicians to select nodes for further evaluation, to help patients to make some decision.

Let's look at nodes more than 10 mm. You already heard from sponsor for those nodes, most physicians will already consider is metastatic cancer, so for those nodes more than 10, most likely you will proceed with biopsy anyway without

Combidex.

The question you probably can ask yourself in that scenario is if I get negative results from Combidex, is that going to prevent me from going to a biopsy. Here is the result. As I showed you, the answer can vary depending on what is the pre-probability, how likely that nodes being positive before you give Combidex.

Before Combidex, if the probabilities are low, then, you get a pretty high assurance if you get an accurate result, it is going to be a true and accurate result, however, as you will see, in my previous presentation, the probability already got up to 75 percent or 60 percent. In that range, if you get a negative result, you only get 80 percent assurance that the node is negative. You still have 20 percent probability the nodes become positive, so maybe in that scenario, most physicians probably would still go ahead to do a biopsy for nodes even Combidex is negative.

So, for that reason, we are seeking your advice to see how we can understand the values of

Combidex for nodes more than 10 mm for helping patients.

Also, where you would emphasize what my assumption here is based on the performance and which we believe has not constantly demonstrated from a clinical development program.

So, based on everything I present today is we believe or the data seem to suggest that Combidex may not have a value for people with a low risk, that patients with lymph nodes larger than 10, the value may be limited, and also this cannot be substituted for the confirmation. Also, we believe there probably is not a good surveillance of the recurrence of cancer, because that population was not studied.

This list and go on and on, and very long, so that is why we are really concerned with the general indication. So, the key question we ask ourself, we are seeking your advice is how the Combidex result will really benefit to patients.

We don't want to leave you a wrong impression that FDA do not care about knowing the

nodes, whether positive or not, we care greatly, however, there is non-contrast agent available. We try to understand what is additional value with Combidex to bring it to the table in addition to the non-contrast agent.

We also understand this test cannot be used as confirmatory test, so we try to understand what role this will play to help a physician help their patients.

We also understand this drug may associate with the potential, the risk, so we want to make clear the use of this drug in appropriate populations, the benefit with risk.

In the later discussion with the sponsor, sponsor proposes four types of cancer which might benefit, that Combidex may have a beneficial effect to the patient, and they also presented those cancers in their presentation.

For the prostate cancer first, I said earlier the Agency do believe for nodes less than 10, Combidex may have a potential value, however, we are struggling with the fact there is only 5

patients from U.S., 5 patients from the European study included in the primary analysis, and the estimate is so unstable from the data I just showed you, we just have no clear understanding what is the true performance of the Combidex for that population.

Also, the same concern applied to bladder cancer, breast cancer, and in less degree to head and neck cancer, because they have more patients, but I would like to bring your attention again for head and neck cancer, most of nodes in European trial, actually, all the nodes in European trial is more than 10.

So, with that, I will conclude my presentation. Thank you very much for your attention. We are looking forward for your guidance to help us to determine the efficacy and safety of this product.

DR. MARTINO: Thank you, Dr. Li.

Questions from the Committee

DR. MARTINO: At this point, I will turn to the committee and give you the opportunity to

ask questions both of the sponsor, as well as of the FDA. As you do that, please raise your hand. Your name will be taken down, and I will call on you as we go around, so please don't yell out, we will acknowledge you in turn.

I would like to ask the first question. I would like the sponsor to make it clearer to me how they actually looked at the MRIs. I am still not entirely clear what they did first, what they did second, and who, in fact, were the radiologists, were they a specific group of radiologists, were there any radiologists, please clarify those issues for me.

DR. GOECKELER: Let me start by saying the question with regard to who made the diagnoses, the order in which that was done was shown in the slides, so that the pre-contrasts were done first, and those diagnoses were committed to. Then, there was the paired, and then after some time there was the post-only.

In terms of who did that, are you referring to the specific specialty of the

radiologist involved?

DR. MARTINO: No, I am trying to figure out did you have two radiologists that looked at all of the films, did you have 100 radiologists? I am trying to understand that element.

DR. GOECKELER: I will address that, thank you.

For the U.S. Phase III trial, there were two blinded radiologists each independently, and the data has been reported both for each individual reader or, as reported today, is the average of the two readers.

DR. MARTINO: Can you also clarify to me what the task of the radiologist was? I know you have shown it, but I need it clear in my own mind what was the charge given to them at each of these interventions?

DR. GOECKELER: I am going to ask Mark Roessel to speak to that issue a little bit in terms of how the radiologists, what they were actually asked to do on each of the blinded reads.

MR. ROESSEL: The blinded readers were

given training and given the guidelines to evaluate lymph nodes, but they weren't given any direction. The nodes were not marked on the images, so they saw the pre-contrast images and any nodes they identified, they circled, and they made a diagnosis.

Then, on the paired evaluation, they did the same thing. They circled the nodes. But the nodes were not pre-identified on the images. The FDA, when we designed the blind read, told us that if we circled the nodes that we had pathology on, that that would bias the readers, so the images weren't marked, and then they did the same with the post alone, they circled the nodes, put an arrow, and gave their diagnosis.

Does that answer the question?

DR. MARTINO: It does. What constituted the denominator for pathology, then, it was the node as seen post-contrast?

DR. GOECKELER: Well, as Dr. Li indicated on his slide, one of the reasons that these patients and nodes drop out along the way is that

the two readings were done on unmarked images, and then the nodes were also taken out just according to standard surgical procedures.

So, then, after all those readings were done, and then the readings had to be matched to the pathology, so in order to be evaluable at the end of all that, the node had to be read on both the pre-contrast image and then identified and read on the post-contrast image, and then it had to have pathology.

So, when you impose those sequential conditions for unmarked images, that is why some of the nodes fall out along the way.

DR. MARTINO: So, then, it was, in fact, the same node. The node had to have been seen on non-contrast, also seen on contrast, and pathology done. That, then, constituted the denominator. Am I clear on that?

DR. GOECKELER: Yes, ma'am.

DR. MARTINO: Dr. D'Agostino.

DR. D'AGOSTINO: I have a couple of questions, first, of the sponsor, and then Dr. Li.

If you look at Slide 9 on the sponsor's presentation, this is page 5 of the handout.

DR. GOECKELER: Is it possible to get that slide?

MR. ROESSEL: Yes.

DR. D'AGOSTINO: It was the sponsor's presentation, I am sorry, the efficacy analysis.

DR. GOECKELER: Could you help us with the title, what it says on the slide?

DR. D'AGOSTINO: Slide 9 is Nodal Analysis, U.S., Phase III.

DR. GOECKELER: Is this the slide you are referring to?

DR. D'AGOSTINO: Yes. I guess I was surprised that there were no confidence intervals given as the presentation was made. Later on, the FDA presentation did have some confidence intervals.

What I am interested in, in this here, is how big were these confidence intervals if you looked at, say, the post-contrasts and compared them with the pre-contrasts for the paired, I mean

certainly the sensitivity doesn't change or they would overlap.

Is there a real differentiation between the specificity or are the confidence intervals so large that it gets blurred?

DR. GOECKELER: I believe we have a slide that has the data with the confidence--if not, I can obtain it, and if someone could pull that data for me, I can provide it to you. I don't have it sitting right here this minute. I believe it was in either the briefing book or if someone could pull the data.

If you give me just a minute, I can provide you the answer to that question. Perhaps we could take another one.

DR. D'AGOSTINO: The other question is, you know, the second question that follows is, as you go to the body regions, which is Slide 11 in this sheet here, how do you make a statement or what kind of statement can be made from the statistics point of view, and then hopefully from a substantive point of view, that it makes sense to

pool these different body regions, because it seems to me in terms of the questions that are asked later on, if we go to particular body regions, it has to be such a small number of nodes involved, and such a small number of subjects, that the inferences are really going to be almost impossible.

So, is there an argument, and I haven't heard it, that says you can, in fact, combine these body regions?

DR. GOECKELER: I am going to ask a couple of the clinicians that routinely image these patients, but, first of all, you will recall from Dr. Harisinghani's talk in the beginning that the mechanism of action of the drug depends on, not a primary tumor, but a physical process of displacement of macrophages within a lymph node.

So, the study was designed with a variety of primary tumors based on the way the imaging agent acts in terms of imaging lymph nodes.

Mukesh, would you like to comment on that further?

Well, with regard to the specific body regions, then, the study obviously was carried out in a mixed populations of patients, and I think that obviously, if you start splitting out a large number of subgroups, the confidence intervals for any given subgroup increase.

I think that looking at the study as a whole, which was designed to evaluate the premise of differentiation of lymph nodes, obviously, that occurred. With regard to the subgroups, I think what is important is that there are consistent trends amongst those subgroups based on the mechanism of action of the drug.

DR. D'AGOSTINO: Moving on, I have just a couple more questions, I obviously don't want to tie up everything here.

In terms of the post-contrast, we were told in the last presentation that not all the nodes were actually used because you want to have a pre- and a post, but there were nodes that were there.

Was any analysis done on the nodes that

didn't enter into the post?

DR. GOECKELER: Yes, there was a separate analysis that was done called the "blinded overread." It is not one of the ones that I described to you, but it involved a much higher percentage of the total nodes.

So, it was again a blinded reading of the nodes, and there was histopathologic correlation of the data at the nodal level for each of the readings, and I can show you--

DR. D'AGOSTINO: Yes, it would be nice to see what the sensitivity and specificity was.

DR. GOECKELER: --what happened in those.

Can you first show the data in terms of the numbers of patients that were evaluated both in the unmarked images and in the blinded overread?

These are the numbers that were evaluated by each reader in the blinded overread, and you can see, based on the various reads, the number of nodes that were read and for which there was histopathologic confirmation for each reader and in each diagnosis.

DR. D'AGOSTINO: Do you have the sensitivity and specificity?

DR. GOECKELER: Can you show me the data on false diagnoses in this, because that essentially relates to, and we can go back then? If you have a slide on sensitivity and specificity, I think you do.

This is the data on the false diagnoses that occurred in the larger reading population. You can see the trends are largely the same as we saw before, about 15 percent with the post-contrast reads, and 25 percent are slightly higher.

We did see a higher variability between blinded readers and the blinded overread for the individual readers.

DR. D'AGOSTINO: It would be nice to see the sensitivity and the specificity and the confidence intervals.

DR. GOECKELER: Do you have the sensitivity and specificity? Get me the numbers, so that I can just provide them.

DR. D'AGOSTINO: Again, maybe we can come

back to it.

DR. GOECKELER: I can give you the numbers, and I can tell you that the trends are very--

DR. D'AGOSTINO: I think it would be very helpful, but I don't want to tie it up here.

My last question is that you did a lymph node as the unit of analysis. There is still the subject, and sometimes in other activities, I don't know about the nodes, but in other activities, when you are looking at the same subject, and you are taking different specimens, and so forth, they tend to be correlated.

So, if you did a person analysis, what would you do with the person, what would you say about the person? Your sample size is greatly reduced. Are there still your inferences?

DR. GOECKELER: Yes, the analyses were also carried out at the patient level, so we have the same data for each of the analyses pre- and post-contrast at the patient level. I am going to ask for a slide one more time.

DR. D'AGOSTINO: Maybe they can produce it later on, the confidence intervals around some of these things I am talking about.

DR. GOECKELER: No, actually, I think they have it. I will tell you and then the slide will be up here in just a second, that the trends we saw in sensitivity and specificity at the nodal level translated through to the patient level also.

Here we go. But this is nodes less than or greater.

DR. D'AGOSTINO: It is really not only the point estimates, but the confidence intervals, what are you actually saying about the individual, how much confidence you have.

DR. MARTINO: Dr. Hussain.

DR. HUSSAIN: I have a question to the sponsor, and it strictly relates to the study design, because I am still not clear about really what the design was, so starting with the eligibility criteria, how were the patients characterized, were there standardized surgery, and was the surgery required each time if it was

prostate or breast or bladder or head and neck, to actually do the same template or do beyond what is normally needed?

And understanding that my specialty, and I am a gyn-oncologist, that there are certain prognostic features that will make you feel or believe that the patient has a high probability of a lymph node positivity, say, in prostate cancer if a guy comes in with a T2 disease, PSA of 50, and a Gleason score, say, of 9, was that accounted for, because in this patient you would think, based on clinical criteria only, without even imaging, that those are very high odds of having this patient have lymph node positivity.

So, with all that taken into account, and if it's not, why not, and what is wrong with having done the appropriate studies, which is accounting for the subpopulations as having adequate head and neck patients, adequate breast patients, adequate lung patients, and so on, to try to make some conclusions from that?

And final question, and maybe I didn't see

it, but what actually was the Phase III trial, what was compared to what?

DR. GOECKELER: Let me take a couple of those and then refer some of those to other people who are more directly involved.

With regard to the comparison, the primary comparator was the paired evaluation as compared to the size-based evaluation on pre-contrast. So, those were the prospectively designed endpoints for the Phase III studies.

With regard to the treatment of the patients and how it was decided which nodes would be sampled, I am going to ask Mark to comment on that. That varied a little bit as Dr. Barentsz said between the Phase III studies and what Dr. Barentsz presented in the post-Phase III studies. So, Mark.

MR. ROESSEL: In the Phase III studies, the entry criteria were patients who had a known primary, who were scheduled for either surgery or biopsy, and who had suspicion of metastatic disease spread to lymph nodes.

There was no direction as to what the surgery or biopsy procedures would be. It was just based on the clinical investigator.

DR. GOECKELER: The standard of practice at the institution.

MR. ROESSEL: Does that answer the question?

DR. HUSSAIN: I guess what I am asking is was it the sense of the treating physicians, or were there guidelines that said if you had this size tumor, this kind of risk?

MR. ROESSEL: No, there were no--

DR. HUSSAIN: So, this was left random to the person enrolling the patient based on their gut feeling whether the patient have--

MR. ROESSEL: There were no guidelines given. The entry criteria were just that, patients with a known primary who were scheduled to have surgery or biopsy, so that we could get pathological confirmation of nodal status.

DR. GOECKELER: Did you have another question, Dr. Hussain, about risk stratification

and predictive of--I am going to ask Dr. Roach to speak to that with regard to relative risk and some of the models and selection of patients who might be most appropriate for treatment.

DR. ROACH: In the sponsor's indication, it specified that patients who were at risk for nodal involvement, so the clinical use for this agent in patients with prostate cancer would be patients at intermediate and high risk disease for whom we have data from randomized trials that demonstrates that treating the nodes is beneficial, and that, in fact, it is important to treat as many of the nodes as possible.

So, this agent would be useful for identifying where the nodes are located and allow us to reduce the morbidity of giving radiotherapy in patients with prostate cancer.

DR. MARTINO: Dr. Levine.

DR. LEVINE: I have several questions. First of all, for the sponsor, are you asking that the individual, that the patient would have two different MRI scans, in other words, your

indication is based on the post-read, so that means that you are asking that patients are now going to have a pre- and a post-MRI? So, that was one question.

My second question, what was in those benign nodes? You know, there are infiltrative diseases of nodes, TB, MAC, et cetera. What were those benign nodes, and what kinds of benign conditions, in fact, fulfill your requirements for benign?

Number 3. This is kind of a funny one, but how did you know that the correct node was actually taken out? Did you do an MRI scan after surgery to know that you really took the right node out?

DR. GOECKELER: Let me ask, in terms of the matching, since Dr. Harisinghani has been involved in a number of these studies, how that is done.

The first part of the question dealt with--I am sorry?

DR. LEVINE: Is the company requesting

that the patient have two different--no, not two different reads--two different MRI scans?

DR. GOECKELER: Two different images, yeah.

DR. LEVINE: And who pays for that?

DR. GOECKELER: In the conduct of the clinical studies, that was required, because the primary endpoint was the comparison of a pre-contrast and a post-contrast read, and I am going to let the radiologists comment upon how they read these scans and how they match the nodes in the clinical studies.

DR. LEVINE: That actually wasn't the question. The question is if this compound is licensed, are you asking that the patient be sent to MRI scan twice?

DR. HARISINGHANI: And the answer is yes, the patient will require two scans pre- and after contrast administration, and in terms of being able to correlate the nodes specifically to the areas on how we know that surgically, we are right, it is an arduous and a difficult task, and for that reason,

we have developed exquisite anatomic maps to which we map the nodes when we read these out, and the surgeons then correlate them to fix the anatomic landmarks, which could be the vessels or bony landmarks, and that is how they figure out where the nodes lie.

DR. LEVINE: All right. Another question was the character of the reactive lymph nodes, what were they?

DR. HARISINGHANI: The benign enlarged lymph nodes ranged in etiology. Most of them are reactive nodes, not pointing to any specific etiology for the so-called reactive lymph nodes, but we had occasional cases of sarcoidosis.

I must say there were no caseating tuberculosis at least in the trials that I have been involved. I am not sure of the general trend, but the benign nodes mainly were reactive and enlarged.

DR. LEVINE: And the sarcoid case fulfilled your criteria as benign, as well?

DR. HARISINGHANI: Yes, that was the case

I showed earlier in the presentation where it behaved like a reactive lymph node.

DR. LEVINE: Have you guys done a cost analysis of the efficacy of this approach given the fact that you are going to do two MRI scans, is there a cost analysis perhaps?

DR. HARISINGHANI: We have not formally studied this in the States, but Dr. Barentsz's group in the Netherlands has actually published their results on cost saving.

Do you want to comment on that?

DR. GOECKELER: Also, just let me comment that although two separate imaging sessions were required in the clinical trials, because of the way that clinical trials were conducted, different investigators in the post-Phase III setting interpret pre and post different ways, and Dr. Barentsz can comment on that also.

DR. BARENTSZ: I would like to comment on the first question first, about cost. We recently published a paper in European Radiology in which we, based on the sensitivity and specificity data,

did do a calculation and analysis on the health care perspective.

If you are including this technique, it will save, in Europe, 2,000 euros per patient, but that is I think not the most important thing. The most important thing, it saves also morbidity. That was not taken in account in that study.

To reflect on the pre- and post-contrast, as among radiologists there are some discussions going on, at this moment, with some newer techniques, you are able to make a sequence which is insensitive to iron, so you can tell the machine "Iron Off," and you can tell immediately after that, "Switch on Iron," and that will substitute for the pre-contrast examination.

Nonetheless, to start in the initial phase for new readers to get some experience, it is advised to use both of those examinations pre and post. I am performing now and studying in the Netherlands, in foreign patients in prostate cancer, a multi-sound study only doing the post just by having insensitive and sensitive sequence.

Also, if you have looked at the data of the sponsor, you can see that if you do the post-read only, it gives a very good result. Perhaps you can comment on that also, Mukesh.

DR. HARISINGHANI: I think, as Dr. Barentsz alluded to, for initial training purposes you need both scans. Once the individual is trained, then, yes, with the existing technology, we can then, as he said, switch on and switch off. Then, it would be possible that you could just do the post-contrast study.

MR. ROESSEL: If I might add, because we need to be clear about labeling for this, as the sponsor, the proposed labeling, the proposed package insert does not specify that you have to do a pre-contrast image and a post-contrast image.

DR. MARTINO: Dr. Mortimer, you are next.

DR. MORTIMER: I wonder if the sponsor could clarify the management of the lymph nodes. Were the lymph nodes just handled in a routine fashion? Were those nodes that were suspicious handled in any different manner to ensure micro

metastatic disease?

DR. GOECKELER: Let me make sure I understand. In terms of obtaining them in surgery or--

DR. MORTIMER: Actually, reviewing them histologically, so to make an analogy of sentinel node mapping, the sentinel node is immunostained.

DR. GOECKELER: I think I understand. The histology was reviewed without knowledge of the image findings. So, they didn't analyze those particular nodes any different than they did any other nodes that were in the study.

DR. MORTIMER: And it was just H and E slicing and--

DR. GOECKELER: Right.

DR. MARTINO: Dr. Perry.

DR. PERRY: A comment for Dr. Li. Your point number 2 about inadequate representation of tumor types, I don't think the sponsor ever attempted to try to do all sorts of tumor types. For many kinds of cancers, this methodology is not necessary. For melanoma, as an example, we have

other staging systems or imaging systems that are quite sufficient.

So, I think it is an unfair criticism to say, when they set out to study four tumor types, that they didn't do all the tumor types. I don't think that is--that is a cheap shot in my opinion, and I don't think that is an appropriate criticism of the sponsor.

For the sponsor, when it comes to education should this product be approved, I think you are focusing on the wrong market. I think if you put the emphasis on physician education, you are really going to miss the mark by a long shot. It is really the tech who gives the medicine, it's not the physician.

I don't know any physician that I have ever seen administer a contrast agent. Perhaps it's different in Europe or in other locations, but if it is, I would like to know that, but it seems to me it is the techs who are going to need to be educated and make sure that they give it the right way, and if you focus on the physicians, you are

going to have problems.

DR. MARTINO: Dr. Brawley.

DR. BRAWLEY: There are a couple of statements that were made in the FDA presentation that I would like to get the sponsor's response to them.

The first is of 152 and 181 patients who received Combidex in the U.S. and the European studies, a third of patients were censored from the U.S. study, and two-thirds of patients were censored from the European study, and not included in the primary analysis.

I would like your response to that, and then I have a couple others.

DR. GOECKELER: Yes, sir. First of all, with regard to the European studies, as I think someone indicated at the beginning, the European studies themselves were initially carried out by the European sponsor with different endpoints, so they were analyzing patients at the patient and group and nodal level.

So, in those studies initially, there was

nodal matching predominantly only amongst the large nodes because it was felt at the time, and you have to recall that these studies were all done seven or eight years ago now, it was felt that the matching could be better done on those large nodes, and I think that is why there is a disproportionate number of large nodes in the European studies.

After the studies were done, the sponsor met with the FDA and agreed that they could take data that was acquired at the individual node level in those studies and analyze it in a blinded read through the same sort of matching procedures, using the same sort of analyses that were carried out for the U.S. study.

So, one of the consequences of that is that there were a large number of nodes removed from those patients that weren't matched on a node-by-node level. So, if you look at the gross number of nodes, and the numbers that were originally--and then the ones that were eventually matched up by two blinded readers and then had pathology, it's a smaller percentage in the

European studies.

DR. BRAWLEY: A couple more follow-up questions.

I am told that there are only 5 prostate cancer patients from the U.S. and 5 from Europe in the primary analysis. Is that true?

DR. GOECKELER: Yes, that's true, and one of the reasons, if you look at both the U.S. and EU Phase III studies, the purpose of the studies was to investigate the ability of the agent to differentiate nodes, malignant from non-malignant.

I think that when you move on to--and obviously, you can subset that a lot of different ways, either by body region or individual tumor, or any number of other ways, and if you do that, certain categories will be large or small, and the confidence intervals will react accordingly.

I think that that is why, when we turn to the issue--and I think those studies did show that Combidex improved the ability to differentiate malignant from non-malignant lymph nodes.

I think that as Dr. Li indicated and as we

indicated, when you move on to the question of where does that provide a clinical benefit, the tumors that we presented on were ones where not only we believe there is a clinical benefit, but also that there was supplemental data post-Phase III, not only on imaging performance, which you saw in the slides that Dr. Barentsz provided, but also on how that imaging performance impacted on clinical utility.

DR. BRAWLEY: So, you are trying to convince the committee that this drug is safe, effective, and efficacious in prostate cancer with a series of 10 prostate cancer patients.

DR. GOECKELER: Well, I wouldn't make the argument about the risk-benefit solely on those 10. I think we have to look at some of the additional supplemental data that is available from other places, such as the publications in the New England Journal and other places.

DR. BRAWLEY: I have also heard that certain source documents, including a pre-defined statistical plan, blinded reader manual, the

original copy of the blinded reader efficacy evaluation, were not available to the Food and Drug Administration.

I would like you to respond to that allegation.

DR. GOECKELER: Well, I think that there have been some questions raised about the exact sequences of events in which the nodal imaging guidelines were developed and finalized, and I addressed that on one of the slides that I presented from the sponsor's perspective. The guidelines were finalized prior to any blind reader, availability of blind read data. Mark, if you would like to expand on that.

MR. ROESSEL: I am sorry, I think you are answering a different question. I think the question was about the prospective plan being available for the New England Journal of Medicine article. Is that correct?

DR. BRAWLEY: That's correct.

MR. ROESSEL: The material that was published in the New England Journal of Medicine

article, as Dr. Li really nicely showed, was done independently of the sponsor. Two clinical investigators, one in Europe and one in the U.S., got together and took 40 patients from trials that they were conducting and did a blinded read.

We don't have, as the sponsor, again, it was done independent of us, on their own initiative, I think is the way Dr. Li put it, we don't have from them a prospective statistical plan or prospective plan for conducting that blind read.

We do have that for our Phase III studies, of course, for our clinical studies.

DR. BRAWLEY: Let me just say parenthetically that that is an acceptable answer, I understand that answer, but I need, and I don't want to criticize this company, Advanced Magnetics at all, I definitely don't want to impugn Advanced Magnetics, and I do want the news media to listen to this.

In my last four years here, I have seen some companies come before this committee, and some companies submit data to the FDA, and what is done

is sort of slight of hand, with selection biases in terms of choosing patients, to try to make one's point that a particular drug or a particular agent works, and we have to be very, very careful whenever we look at data to understand exactly what the source of the data is and the validity of the data, and most importantly, the selection biases of the patients going into the data before we can make a decision.

That is a point that has been missed repeatedly in a number of newspaper editorials about drug approval recently, so that is the basis for my question. You, sir, you did give me an acceptable answer, and again I want to state I don't want to at all impugn your company.

Last question. I heard that a patient died getting this contrast agent. I thought I heard that the patient got the contrast agent in a facility that was not able to treat an allergic reaction.

Is that true?

DR. GOECKELER: Mark, you can comment on

the facility, and I am going to ask Dr. Bettmann to comment on sort of the guidelines and regulations regarding what those sorts of facilities are required to have.

MR. ROESSEL: The facility in question was a free-standing MRI unit. We made sure in our site qualifications for doing clinical trials that equipment was available to treat any reactions that occurred. They did have emergency equipment, which I think is what you asked me, they did have it available. Apparently, they didn't choose to use it.

DR. BRAWLEY: That, too, is an acceptable answer, I just want to go on the record as saying.

DR. MARTINO: Dr. Houn, did you want to make a comment?

DR. HOUN: Yes, just to clarify when a sponsor obtains right of reference to studies to support their application, they have to be able to provide to FDA access to underlying data to provide the basis of the report of the investigation.

This did not happen with the New England

Journal study, and also just as a reference to the committee, FDA didn't mean to give a cheap shot in terms of the numbers of people enrolled, just in previous approvals for ProstaScint, prostate cancer only imaging drug, there were 152 people entered into the analysis only with prostate cancer, and there were 183 that were followed for the open label efficacy study.

When we did NeoTec, a lung cancer detection for non-small cell lung cancer, there were 228 entered into the analyses. When we approved PET-FDG, that got a broad indication for all kinds of cancers. There were 1,311 people entered into the analyses.

DR. MARTINO: Dr. Reaman.

DR. REAMAN: Just a question again about the eligibility criteria, and I guess to somewhat follow up on the issue of selection bias.

You stated that any patient with cancer who was at risk for developing lymph node metastases were eligible for this study, and they were eligible based on whether or not they were

going to then have either a biopsy or a surgical procedure.

So, how was the decision as to whether they were going to have surgery or a biopsy procedure made, by equivocal or positive radiographic studies before they were entered on this study, or did they have palpable adenopathy? Other than the breast cancer patients in the sentinel node biopsy, I am still not satisfied that this isn't a selected population.

DR. GOECKELER: I will ask Mark to expand on that, but I believe it's the case, and Mark can verify, that the image findings, the post-contrast image findings could not play a role, and were not available to the physicians in making those assessments.

So, the physicians did not have any post-contrast image findings on which to base that assessment of whether the patient then went on to surgery or biopsy. It was done based on the normal clinical information that would be available to make that decision for every other patient.

DR. REAMAN: So, radiographic studies weren't part of the clinical information?

DR. GOECKELER: Well, I think that the pre-contrast, you know, you could have a CT or an MRI pre-contrast, but no post-contrast image findings.

DR. MARTINO: Dr. Bradley.

DR. BRADLEY: I have a couple of questions maybe for the authors of the New England Journal article, following up on a question by Dr. Li.

How did you select those 40 and 40 patients from a group that was 3 times larger? I mean selection bias kind of comes to mind, but what selection criteria did you use?

DR. HARISINGHANI: It is 3 times larger now, but it wasn't then. The selection was consecutive patients who were scheduled to undergo radical prostatectomy both at the U.S. and at the European site.

They were of the intermediate and high-risk category, I must admit to that in terms of the patient selection.

DR. BRADLEY: And then a follow-up question. You showed some very nice images of very small nodes, one of you, or positive nodes. With 5-mm cuts, and no way of guaranteeing that you are in the same place for the second scan, how do you know you are comparing the same nodes pre and post, particularly not for you, but for the chest where you have respiratory artifact?

DR. BARENTSZ: In our New England Journal paper, we used 3-mm cuts in the obturator plane, and we used 5-mm cuts in the axial plane. We performed a combination of sequences which visualized the anatomy and also a sequence which visualizes the iron, and based on also a 3D sequence which we performed, we were able to compare the pre and post and exactly locate the lymph nodes where they were, so we could make a very accurate match on the 3-mm and 5-mm images.

Also, we located the nodes in relation to the vessels. So, I agree with you that localization and the location of lymph nodes is very important.

DR. BRADLEY: So, the slice location of 3-mm slices was accurate, looking at the other anatomy?

DR. BARENTSZ: Absolutely.

DR. BRADLEY: A follow-up question. On the 15 percent--this may not be for you guys--but 15 percent false positive and false negative, we have talked a little bit about what might cause a false positive. What about false negative, any thoughts, did you do an analysis of why they were false negative?

DR. HARISINGHANI: I think there are two issues here at least from our study. I would let Bill answer for the general part, but the false negatives are mainly as we are talking of nodes which are smaller than 5 mm, then, the current resolution of our scanner only enables us to be confident at a certain level, and that could account for the false negative reads.

DR. BRADLEY: Then, one final question for the sponsor. Why did you choose a 0.2T Hitachi when this is clearly a magnetic susceptibility

agent? Is it so sensitive that a gradient echo at 0.2 shows you what you see at 1.5? Also, I suspect, having read all of this, that that was also where you had your single death, is that correct?

DR. GOECKELER: I am going to have to ask Mark or Paula to comment on the specific imaging equipment. Please recall that the death was in a liver imaging study, not in a lymph node imaging study.

DR. BRADLEY: Right. I saw the physician of record on that, who happens to own a bunch of low-field magnets in Ohio. I am just wondering if it is the same case. But why include a 0.2 at all?

MR. ROESSEL: We tried to include in the Phase III clinical studies, we didn't specify the imager to be used. There was no requirement for it to be a 1.5T or 0.2T. The fact is we provided the Agency with the information on the types of imaging equipment used, and I think most of them were 1.5T, the vast majority. It was a very, very small, I think one or two that used 0.2T in the studies.

DR. BRADLEY: Just to follow up, was the

0.2 Hitachi also where the death occurred?

MR. ROESSEL: That, I don't know.

DR. MARTINO: Ladies and gentlemen, we are running short of our allotted time, but I appreciate these questions as important, and that is why I am giving you a little more time in this part of the meeting.

That being said, I would ask those of you asking the subsequent questions, please be sure that your questions are necessary to your thinking about the efficacy and the approval of this agent, and are not just purely for your perhaps intellectual curiosity.

Dr. Giuliano.

DR. GIULIANO: I am a surgeon, Dr. Martino. We have limited intellectual curiosity, so my--

DR. MARTINO: I know.

[Laughter.]

DR. GIULIANO: Therefore, my questions will be brief. But I am struggling as a surgeon through these documents. We say the surgical

procedure was not altered, the post-enhancement images were not available.

How did you instruct the surgeon to remove the Combidex abnormal enhanced lymph node? He or she had to know what that node was, where it was. It had to be labeled as such. So, on a node-by-node analysis, I think that introduces a surgical bias because as any surgeon knows, it is easier to find a positive node than a negative node.

In addition, using the node-by-node analysis, what happens with nodes not seen on MR that are removed? For example, if this agent did not alter your surgical operation, the patient with a prostatectomy may have had a pelvic lymph node dissection, and there was one node that had been identified on your preoperative images or an axillary dissection for breast cancer, and there are one or two nodes, and 15 or 20 nodes were removed.

If you look at the 1 or 2 nodes, which had to be seen on the image, had to evaluated

histopathologically, and they correlated, let's say they were both negative, what if all of the remaining nodes were positive or one of the remaining nodes was positive, how was that dealt with statistically or in your presentation? I could not understand that.

DR. GOECKELER: I will ask Dr. Anzai to talk about the nodal matching and how those nodes were identified, and how imaging was or wasn't used in the identification of those nodes.

DR. ANZAI: I am the radiologist involved in Phase II and III clinical trials. Your comment is absolutely right. This was the hardest trial that we ever had in Radiology, that I personally have to have images going to OR when the patient is in operating site, and we have to ask a surgeon to make stitches on a certain anatomical level.

For example, a head and neck radiology, I have to ask the surgeon to make stitches on the submandibular--this is the jugular vein, so in between this lymph node is the lymph node that I am seeing in imaging, and it was very labor intensive.

Many of the radiologists have to be in the OR with this graph, and the surgeon to identify, correctly identify those lymph nodes on imaging, or lymph node in a patient, so the pathologist would identify this is the exact lymph node that we saw in imaging.

That is why the sample size was so small, because we have to have a certain confidence that the imaging on the lymph node is matched with final pathology. That is why the size of the lymph node that is seen in all the cancer patients are small, but this is such a labor intensive study, but we did as much as possible to correlate imaging on a lymph node with surgical pathology by being in the OR.

The second question for statistics, maybe Mark can comment.

DR. GOECKELER: I think that the issues that have just been identified by Dr. Anzai and others are the ones that account for the analysis that Dr. Li showed, where you start out with a large number of nodes and then if you are going to

require evaluation on unmarked images to avoid bias in the reading of the data, then, you lose some nodes along the way, because the readers don't all identify the same nodes every time they read.

That is why you see some of the nodes or the numbers dropping off at every level. We tried to address that in part by looking at another read that involved the blinded overread, which are a much larger percentage of the nodes.

DR. GIULIANO: Maybe I wasn't very clear about that. My question is if the labeled node from the operating room is the one identified on the MR, and histologically evaluated, and is positive or negative or whatever the correlation is, but other nodes that were not seen are positive, was that counted as a false negative or was that not counted because the other nodes were not seen on MR?

DR. GOECKELER: No, the primary analysis was at the nodal level, so those numbers that were presented were at the nodal level. There were other analyses the data tracked very closely at the

patient level where you can look at the patient level also.

DR. GIULIANO: Thank you.

DR. MARTINO: Does that answer your question, Dr. Giuliano, because I am not sure that it did.

DR. ANZAI: Let me add one thing. I think your question that the lymph node that not identified on the MRI, how do we handle that. I think a nodal level correlation, we didn't look at those lymph nodes were pretty not pre-identified by imaging, but a patient level analysis, if, for example, MRI showed all the normal lymph node, but pathology somehow find one positive lymph node that not identified MRI, I think that was considered to be false negative.

DR. GIULIANO: Perhaps you could share that patient analysis, would that be appropriate, Dr. Martino?

DR. MARTINO: Well, to be honest with you, I think at this point you are going to have to make your decision realizing that the data that you need

perhaps are not presented to you right now. I think that may be one of the issues.

Dr. Bukowski.

DR. BUKOWSKI: I am trying to understand the efficacy and benefits of this approach, and there was a statement made that there is a decrease in morbidity when you apply this particular product.

Can you help me understand what the implications are? Are you implying that there will not be a need for surgery if there is an identified positive node, or that there will be then a percutaneous biopsy done, and, if so, what is the likelihood of being able to biopsy the small nodes that you are referring to, less than 10 mm, using techniques not only at academic centers, but centers elsewhere?

DR. BARENTSZ: You raise a very good point, and I would like to address a little bit to our New England Journal paper, which is different from the Phase III study in that way, that in the New England Journal paper, we were able to--we were

allowed to include data which were obtained from the Combidex MRI into clinical practice.

So, that paper shows better the real clinical effect of what this contrast agent can do. So, if we found an extra node, we were allowed to tell to the surgeon, and I again agree with you, communication with the surgeon where the node is, is very important.

Mukesh and I, we started by making some nice schemes, which have been used by the surgeon, and sometimes we, well, we went to the surgery room. So, we added the information of the MRI for the surgeon, and we asked our surgeon how this scan, how did this really change his management, did that decrease the extent of surgery.

Actually, the black nodes, they are normal, and if you have a high sensitivity and a high negative predictive value, but if you have both very high, as what we obtained in our paper in the New England Journal, both on the patient and as on the nodal level, that means that the risk after an MRI, that the patient has a negative lymph node

is extremely high.

That means the number you are missing is extremely low, and that current threshold, our urologist advises, but I would like also to have one of the urologists to speak on that. That is very important clinical information which may actually decrease the number of lymph node dissections.

If you have a positive lymph node, it always must be confirmed histopathologically. If it's large, 7 mm, 6 mm, or 10 mm, you can do that by image-guided biopsy. If it's smaller, you have to tell the urologist the node is down there, and he can remove it.

Perhaps the urologists can make also some clinical remark on that. Comment about the clinical use, how this technique can be applied, what will you do if you have a negative MR Combidex, what will you do if I am saying it's a positive lymph node.

DR. KALINER: Well, first of all, any information that I give as a clinician, first of

all, I am a urologist for the last 16 years at George Washington University, and recently joined Cytogen as the Vice President of Medical Affairs, so I have a lot of experience in surgery and urology.

Any information I can get that helps me identify whether there is more extensive disease or not is extremely important with these patients. So, in the case, if I have a negative Combidex scan, first of all, I wouldn't do a Combidex scan unless it is somebody that is intermediate to high risk, as many of these patients were, so they are stratified by risk to begin with.

So, this is somebody that has a negative Combidex scan, we still would perform the lymph node dissection, but if there was a reason to look in an extended area, which we know pathologically does occur, then, that scan can help guide us to do that.

On the other hand, if we did find something ahead of time, we may be able to eliminate doing an invasive procedure by performing

a biopsy or perhaps a laparoscopic lymph node dissection as opposed to an open procedure. There are a variety of ways to look at doing that.

Any way that I can get more information to help prevent an invasive procedure when it is not necessary is extremely important.

DR. MARTINO: Dr. Dykewicz.

DR. DYKEWICZ: I have two questions regarding safety and adverse events. The first is whether slowing the rate of the infusion as proposed will really reduce the risk of hypersensitivity reactions.

In the sponsor's presentation, there was data presented showing that the number of adverse events were reduced with the use of that administration method, but, of course, adverse events could include both hypersensitivity and non-hypersensitivity events.

Hypersensitivity events are the ones that are potentially going to lead to fatalities, so that is where I have my greatest concern.

The FDA analysis was that the overall risk

in severity of hypersensitivity reactions was actually not reduced, and they presented one data on Slide 21, Presenting Symptoms of Hypersensitivity Reactions, that showed that at least in terms of urticaria, the rate even increased with slowing the infusion rate from 63 percent with the bolus to 85 percent.

Some of this I think is probably just a result of the signal of having a relatively smaller population with the bolus group, but from the standpoint of the sponsor, are you of the belief that the slower infusion rate will significantly reduce the risk of hypersensitivity reactions?

DR. GOECKELER: I think the issues are related to risk and management, and I am going to ask Dr. Page to speak to that, please.

DR. PAGE: The most telling data about this are to look, not at all hypersensitivity reactions, which again tended to be--this is an iron product, so that the notion is that any exposure in the bloodstream is likely to cause some activation of mediators, so you are going to see

some flush.

So I would contend that the notion of hypersensitivity is probably too broad. That is what we are looking at, it is a hypersensitivity reaction, and in that sense, I agree with the statement that it is not clear that dilution will reduce rates of hypersensitivity, but I believe the data show convincingly that they will reduce severe both all AEs, as well as hypersensitivity AEs.

In the case of bolus, there were 3 serious adverse events out of 131 patients. That is a rate of 2.5 percent. In the case of diluted, there was, in fact, only 4 out of 1,200, and, of course, that is a rate on the order of 0.3, so there is a log order difference in the rate of severe adverse events. That is one piece of information.

The other is we know that in patients who are having an immediate hypersensitivity reaction, you can turn off the infusion, the reaction goes away, and you can restart the infusion. So, it is not only the accrued rate of all the reactions. The real question is severe, and the reason is can

you intervene.

DR. DYKEWICZ: The second question, which actually dovetails with that, and a question that Dr. Brawley had asked about earlier, is the acute treatment of the serious hypersensitivity reactions.

Were any of these patients given epinephrine?

DR. PAGE: I believe none were. Mark, correct me if I am wrong there. Some were given steroids, of course, some were given albuterol in one case. As far as I recall, there was no epinephrine given.

DR. DYKEWICZ: Well, this is no indictment specifically of the sponsor, but for discussion later, I would raise the point that the treatment of choice for a serious hypersensitivity reaction would be epinephrine.

DR. PAGE: And would you say that is true if there was no hypotension and on cessation of infusion, and there is no acute respiratory compromise?

DR. DYKEWICZ: Potentially, yes. Studies have shown that in anaphylaxis, delay in the administration of emerging anaphylaxis is associated with an increased fatality rate.

Obviously, this requires some clinical judgment depending upon the clinical presentation of the patient, but I would say that, in general, if you have patients with serious hypersensitivity reactions, that none have received any epinephrine, that is sad in my opinion as an allergist.

But again, this is nothing specific for the sponsor of this agent. I think it is reflective of the standard of care generally.

DR. GOECKELER: Dr Bettmann.

DR. BETTMANN: I wanted to comment as a clinical radiologist. I think your point is very well taken. My recollection of the data are that the only patient that was given epinephrine was the one patient who died, and that patient was given in a very delayed fashion, so it was inappropriate.

Again speaking as a clinical radiologist, it gets to the point of who treats these reactions

and how, and how are they trained, and that gets back to what Dr. Brawley touched on about why was the study done, that one fatality, in a place where the reaction couldn't be treated appropriately.

I think the answer is simply that there are, the American College of Radiology has very clearly stated that contrast should not be injected where there isn't equipment to treat reactions that are potentially fatal and where there aren't people who are ACLS trained.

So, you started by saying it's not an indictment against the sponsor, I think perhaps it's an indictment against clinical radiology. There is no question that patients should be treated appropriately, there is no question that the appropriate treatment is known. It is a matter of linking those two.

I think that is a question that sort of is unfortunately way beyond Combidex.

DR. MARTINO: Thank you.

Dr. Rodriguez. For the rest of you, there is only three of you. Please be brief and

succinct.

DR. RODRIGUEZ: I just want to be very clear about one issue. One of the committee members previously said that the company obviously did not intend this product to be used in all malignancies.

As I read the application or in this proposed indication, however, it is worded exactly the same in both the FDA presentation and the sponsor, and it states that it is to assist in the differentiation of metastatic and non-metastatic lymph nodes in patients with confirmed primary cancer who are at risk for lymph node metastases.

So, to the sponsor, are you, in fact, requesting that the FDA approve this product for broad application in all malignancies?

DR. MARTINO: I will take a yes or no answer to that. That is all that is necessary in my mind.

DR. RODRIGUEZ: That is all I need.

DR. GOECKELER: The indication was based on the Phase III clinical trials. I think the FDA

and the sponsor --well, that is the indication that is being sought, yes.

DR. MARTINO: Thank you.

DR. D'Agostino. Succinct and brief.

DR. D'AGOSTINO: I will be very brief. Just to go back to some of the questions I raised earlier in here, it seems to me, and the sponsor can say yes or no, that what we are dealing with is trying to evaluate efficacy based on not all the subjects available, not all the nodes available, if there is differences between the pre and post in terms of sensitivity and specificity, it is basically on a per-node basis. It is not based on per type, body region, and it is not based on a per-person basis.

I don't see any justification for combining the body regions by statistical criteria. I didn't see anything on what happened to the nodes that weren't in the paired analysis, and I think on the per-patient basis, you have such a small number of patients, that we probably don't have any significance on sensitivity, specificity, and

disposition of the patient.

A yes or no from the sponsor would be interesting.

DR. GOECKELER: There were a lot of questions. First of all, with regard to the body regions, those weren't combined. The data sets were for the entire populations. They were subgrouped out after the fact.

So, the primary analysis was for differentiation of metastatic from non-metastatic lymph nodes based on the entire population. That is why the indication that is being sought is written the way it is.

With regard to the question of where there is a clinical benefit to that, I think that is why we presented additional data from additional studies in specific cancers.

DR. MARTINO: Mr. Kazmierczak, the last question.

MR. KAZMIERCZAK: Thank you. My one question on generalization was already asked and answered. In the FDA's presentation, they

indicated that certain patients were excluded on the basis of pretreatment with radiation or androgen ablation.

I would like to have the sponsor comment on whether the FDA statement that Combidex should be used for newly diagnosed patients as a restriction is reasonable.

DR. GOECKELER: I think it is the population that has been studied in clinical trials, yes.

DR. MARTINO: Thank you, ladies and gentlemen. I will give you a five-minute break only. I will start without you.

[Break.]

Open Public Hearing

DR. MARTINO: The next portion of this meeting is the open public hearing. Those of you who have requested permission to speak at this portion of the program, I will remind you that you have five minutes only. Please identify yourselves, and there is a microphone in the middle of the room, which is the one that you will be

using.

I need to read a statement, so that you all understand the purpose of this portion.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the 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, your lodging, or other expenses in connection with your attendance at the meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the committee

if you do not have any such financial relationship. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

MS. CLIFFORD: Our first speaker is Mr. Curtis Holladay.

MR. HOLLADAY: I do not have any financial affiliation with the sponsor, however, my travel and lodging is being paid for.

I am Curtis Holladay, a 73-year-old prostate cancer survivor of seven years, here this morning to tell you about my recent experience with the Combidex test. As you will see, this diagnostic tool was crucial to understanding the stage and disposition of my prostate cancer thereby allowing the opportunity for experts to prescribe the appropriate therapy.

Diagnosed in 1997, I subsequently underwent radiation therapy, both seed-implant and external beam. After it had become evident that the radiation therapy had failed, a hormonal therapy was employed, but discontinued after a year due to

liver toxicity.

During this time, four bone scans and two computed tomographies revealed no evidence of metastasis. In order to determine my eligibility for local treatment, the question of metastasis to the lymph nodes had to be answered.

Internet searches and consultation with Dr. Stephen Strum led to the Combidex technology as offering the most reliable test. Although one of the Phase III clinical trials was run in the U.S., it was still not available here, but it was available at UMC St. Radboud at Nijmegen in the Netherlands. It was under the direction of Dr. Jelle Barentsz whose work was reported to be outstanding. The importance of the information to be gained left me no choice but to travel to the Netherlands at my own expense.

Our party arrived at the Amsterdam Airport early morning and drove to Nijmegen for me to receive the Combidex contrast injection that afternoon. The MR scan was performed the next day allowing the required 24-hour waiting period.

There was no pain or unpleasant effect from the Combidex injection.

Dr. Barentsz reviewed with me the MR scan images. He pointed out images of lymph nodes on my left side were white or illuminated, indicating metastasis. Images of the lymph nodes on my right side were dark or black, indicating that they were normal, free of metastasis.

Although I had hoped for a better outcome, it was better to know than not to know. The Combidex test made it clear that a local therapy was no longer an option and that a chemo-based therapy would be necessary to check the metastasis.

I would hope my personal testimony helps persuade the FDA to approve the Combidex test for use in our country as it becomes more evident every day that we need to bring available tools and resources to bear on this unrelenting disease.

Thank you for the opportunity to make this statement.

MS. CLIFFORD: Thank you, Mr. Holladay.

Our next speaker is Barbara Lestage.

MS. LESTAGE: Good morning. I am Barbara Lestage. I am a 9-year breast cancer survivor from Wrentham, Massachusetts. I am currently Chair of the American College of Radiology Imaging Network's Patient Advocacy Committee. I served for two years on NCI's Central IRB, and also was Chair of NCI's Director's Consumer Liaison Group for three years.

I was invited to speak today by Advanced Magnetics, which is covering my expenses.

I don't know how many of you have been personally diagnosed with cancer and understand, not only what a frightening time it is or the confusing one it is, as well. Living in the Boston area, I was fortunate to have three world renowned physicians to advise me, but unfortunately, they did not agree on what my treatment should be.

I learned during this very difficult time that in spite of all the progress which has been made, treating cancer is often as much an art as it is a science, because there is still so much that we do not know.

Obviously, for each individual patient,

the goal is to gather as much information as possible, so that the treatment can be tailored to their particular cancer with the goal of neither undertreating nor overtreating the patient, which can lead to unnecessary side or late effects and adversely affect the quality of life.

In my case, two of my physicians wanted me to have a nodal dissection, but my surgeon thought that because my primary tumor was so small, it was non-high grade, and there was no lymphatic nor vascular invasion, that the morbidity, which could be caused by a nodal dissection, would outweigh any information which might be gained by doing one.

I can't tell you how many agonizing hours and days I spent going over, not only the conflicting opinions, but the literature before finally deciding against a nodal dissection.

Now, nine years later, it seems pretty clear that the decision I made was the correct one. I spent many years wondering and worrying if I had made the right decision.

When I heard about the trial using MRI and

Combidex, I thought to myself how wonderful it would have been to have been able to have such a scan. While in my case, it would not have made a difference in my treatment, it would have given me enormous peace of mind.

Obviously, for many patients, it would help determine, not only the extent of their treatment, but the type of treatment that they would have.

I suppose the question could be asked why do we need a new way of determining nodal status when we already have several, but I think there are three reasons why we need one.

First, is that the current method of determining that based simply on lymph node size alone has an accuracy rate of only 68 percent, while the stated accuracy rate for MRI and Combidex is 85 percent.

Second, is that for many patients, a nodal dissection requires a second incision, which can sometimes leave the site numb for years with prickling, tingling, pain, burning, and often

leaves the muscles weak.

The third is the risk of lymphedema, which for breast cancer patients is about 15 percent of those with a total nodal dissection and is severe in 1 to 2 percent of those women. Women who have had a nodal dissection for the rest of their lives have to avoid anything which might cause lymphedema to develop.

This means they must constantly remember to avoid hot baths or showers, sunburns, harsh soaps, insect bites, tight sleeves, or even playing with a beloved cat or dog. More importantly, they must avoid having their blood pressure tested or receive any sort of injection or blood draw in the arm on the side where they had their nodal dissection.

A friend of mine was diagnosed with cervical cancer in 2001. She was given a radical hysterectomy and had 35 nodes removed, all of which turned out to be negative. She didn't have any problems at first, but then her left leg became infected, which has led to chronic lymphedema.

Each day she must spend an hour with her legs in the air, massaging them to try and get the fluid out. Then, she must wear compression hose for the rest of the day, and she must bandage her legs every night before bed.

Flying is possible only if she can stand and walk for most of the flight, and she must constantly carry antibiotics with her in case of infection. She used to wind surf and hike, but now because of the risk of a scratch or poison ivy, those and many other activities are no longer possible.

Because of the medical insurance she has, the physical therapy and the compression bandages often have to be paid for out of pocket.

Because of my two years on NCI's Central IRB, I understand the difficulty of balancing the risks and benefits of new drugs while trying to provide the best possible treatment to cancer patients.

We talked this morning about the value of physician education and technician education, and I

would suggest to you that equally important is patient education. I feel very clearly that as long as the risks are explained to a patient, they should have the opportunity to have a new drug if they feel that the potential benefits outweigh the potential risks of doing so.

I understand that Combidex and MRI is not risk-free, but I believe the risks to be reasonable, and that for many patients, they are clearly outweighed by the benefits of a new, more accurate, non-invasive way of determining nodal status.

Thank you.

MS. CLIFFORD: Thank you, Ms. Lestage.

Our next speaker is Mr. Mendinger.

MR. MENDINGER: My name is Larry Mendinger. I am a home builder from Ashland, Oregon, and Combidex paid for me to fly here, however, I can tell you that is a negative investment for me, because I am missing three days of work.

I have prostate cancer. I was diagnosed,

oh, three years ago or something like that. It should have been four or five, but my doctor didn't happen to notice what my PSA was doing.

I went through some treatments, which seemed to stave off the growth of the tumors, and my PSA kept bouncing around for some time. In the last eight or nine months, I have had--well, I should say before I had Combidex, myself and my insurance company probably spent $18,000 on everything from ProstaScint to CT scans and PET scans, and all that stuff.

It all showed, well, we really don't think so, that you really have anything to worry about, we can't seem to see it. So, when I finally--I was feeling very uncomfortable and my PSA was going up drastically, last summer my doctor heard about the Combidex, and he sent me to Dr. Barentsz's place in Nijmegen--did I say that right, Nijmegen, thank you--beautiful place, and very enjoyable trip.

I had the Combidex and I sat down in my shirt and kind of half-naked, but afterwards, and looked at the scanner with the doctor, and there

was absolutely completely, black and white, exactly what was wrong with me. I have to say I can't tell you as a patient what that means when you actually know what is going on in your own body,when all these other people, with all this money spent, can't tell you.

The other thing I want to say is I did not go for a surgical procedure to begin with, because my urologist said, well, you need to have surgery right away when I first had my diagnosis, and I went home and I downloaded--I finally found a procedure diagrammed on Johns Hopkins University website, and I looked at that and I said, you know, I am not a surgeon, but that looks like brain surgery to me, no thanks.

So, I have been looking for a way to remain intact as a man, and this was really important. You guys need to approve this.

MS. CLIFFORD: Thank you, Mr. Mendinger.

Our next speaker is Ann B'rells.

MS. B'RELLS: I am Ann B'rells from Schenectady, New York, and I want to thank you for

having me. I have no financial interest in the company and paid my own way to the meeting. The only consideration I am taking is ground transportation back and forth to the airport and maybe lunch.

I come to this hearing as a breast cancer survivor for three years. Three years ago, I was diagnosed with breast cancer during a routine mammography, and ultrasound proved it, an aspiration revealed cancer, which was small and fairly well defined, and I was told at that point that a lumpectomy was in order.

In order to find out how the cancer was spread, it was recommended that I have a sentinel node biopsy also at the same time. No other way of identifying the lymph nodes was suggested to me because of the comments that you have heard earlier today.

After the surgery, I was lucky and the sentinel was clear of cancer. Unfortunately, so was all the other material they had taken, and ultrasound showed that they had missed the lump,

and they had to go back in and get it.

I was recommended for radiation and Tamoxifen or Arimidex, and I chose Arimidex.

The reason I am here talking to you today is that at the point of after the second surgery, when I had to make a decision about treatment, it was quite clear that there was no way, a non-invasive way--and you have just heard all about the problems of taking all the lymph nodes--available to me even though there was a several month delay between the operations.

There was no way I was going to have general chemotherapy as opposed to Arimidex or Tamoxifen because of the side effects and possible mortality from that.

At this point, the only diagnostic tools I have are the usual physical exams, mammograms, breast ultrasounds, and uterine ultrasounds. I have had a couple of scares as everybody has, and I can't repeat often enough the emotional and other physical effects from just the fear.

To be able to have known after the second

lumpectomy, to have had a test that my doctor would have recommended, and I think that he would have recommended this one, would have been wonderful.

I just want the committee to understand that even though I was treated only three years ago, that there are always complications that come up, and that the ability to understand what is going on with lymph nodes without actually taking them out would be wonderful.

The second comment I have is that although sentinel node removal is a much milder activity than taking more of them, it still carries a small risk, and that risk leads you to the same preventative activities of only having one arm to give blood, et cetera. So, that is another reason that it would be wonderful if the sentinel, which also misses, what is it, 15 percent of the active cancers, could be eliminated.

So, I thank you very much for your attention.

MS. CLIFFORD: Thank you for your comments, Ms. B'Rells.

Our next speaker is Tom Brady.

DR. BRADY: I am Tom Brady. I am from Boston. I am a Patriot, but I am not the quarterback. It is a problem I have periodically.

I am here with no financial interactions with the company. They have never supported my research. I am actually the Director of Radiology Research at the Massachusetts General Hospital and Professor of Radiology at Harvard Medical School.

I came here for the first time in my life to address the FDA, because I felt that this was important enough to take a day off from work--I appreciate the prior speaker saying you can't pay for a day off of work--and come here to say a few things.

The first is there is no perfect pharmaceutical or contrast agent. The FDA, in its wisdom, 40 or 50 years ago, did not approve a drug called thalidomide, which saved thousands of lives and deformities. That drug is currently I believe approved for a number of applications around the world including leprosy and other vascular

problems.

I was really impressed by the data that was generated in Europe and at the MGH and presented in the New England Journal of Medicine primarily because, as a radiologist, there is really no way to evaluate small lymph nodes, whether they are benign or malignant.

2-deoxyglucose, which is a PET agent, which was not commented on here today, is extremely good especially for looking at larger lesions, but the ability to identify with high accuracy disease in small lymph nodes can significantly change the management of patients.

I concur with the studies from Europe on the cost efficacy. We will see more of those studies from the MGH coming out soon, and we believe that it will, in fact, demonstrate that at a high degree of efficacy.

So, in summary, I thank the committee for this opportunity. I don't want to take additional time, but I think that this agent should be approved. Thank you.

MS. CLIFFORD: Thank you, Dr. Brady.

DR. MARTINO: The Committee would like to thank all the public speakers and all those of you who are in the audience who perhaps would care to speak, but have chosen not to do so. We do appreciate your being here.

I will tell you as a clinician, particularly those of you who are patients, and who understand these things from a very personal perspective, that the Committee welcomes your being here and appreciates you putting things in a certain perspective for us. So, please know that we value your contribution.

We are now going to turn to the discussion portion of the meeting, and this will end with ultimately an actual vote that will be taken. So, realize that the vote will be the last part of what we are going to do this morning. You will have opportunities to discuss this before we actually request a vote of you.

Dr. Ownby, I have been told that you had some burning question that I somehow ignored. If

it is still burning in your heart, I will allow you to ask it before we proceed.

DR. OWNBY: It was answered previously.

DR. MARTINO: Thank you.

There are a series of questions which have been provided to each of the committee members. We are going to focus, however, on truly the very last one, because I think the other three are somewhat encompassed within the final question.

Before I do that, I just want to remind this committee of what it is that is being sought here today from the maker of this agent. It is an indication for intravenous administration of this agent in differentiating metastatic from non-metastatic lymph nodes in patients with confirmed primary cancer who are at risk for lymph node metastases.

I do want you to recognize the nature of those words. They are not asking for a particular tumor, nor for any particular size of lymph node. We have to deal with the question and the request as they have posed it to us. Please keep that in

mind as you go through the next deliberations.

The question that the FDA wants us to answer for them, and for those of you that are guests to this committee, realize that this committee is advisory to the FDA. We give them our opinion. They then take that into consideration as they make final decisions.

Most of the time I think they take us quite seriously, however, so there is weight to your thoughts and to your vote.

Question No. 5. Do the data demonstrate that Combidex is safe and effective for marketing approval based on the sponsor's proposed indication?

If yes, are there post-marketing studies you would recommend to them? If no, do the data demonstrate that Combidex is safe and effective for marketing approval for any other indications?

If yes, please describe the patient population and clinical setting for which Combidex would be indicated, and, if no indication is supported by the current data, please recommend

what additional studies or data are needed.

It is on these questions and their nuances that I would now like to invite you to give us your thoughts.

As we did before, please raise your hand. I will recognize you in turn.

Who wants to start? Dr. Brawley, you are always a good one to get us going, so I think I am going to turn to you.

Committee Discussion

DR. BRAWLEY: I guess I will start out. I just wrote a couple of things while I was hearing some of the public comment. My concern is the guy with prostate cancer who is told that he has positive nodes by the scan, but in reality, the nodes are negative, and he does not get a radical prostatectomy because the scan was wrong.

If you go through the mathematics that we just had, and this incredible mathematical thing, talking about epidemiologic terms, such as sensitivity, specificity, positive predictive value, negative predictive value, and another thing

called accuracy, which is a different kind of accuracy from what the lay people talked about, that is going to happen.

You are going to have a guy who has negative nodes, who gets this test, and he is told you have nodal positive prostate cancer. The guy does not get a radical prostatectomy which could save his life maybe, but it would be the end of prostate cancer for this man if he got that operation. I can guarantee you if we test 10,000 people, there is actually going to be a handful, more than 20 or 30 men, maybe over 100, who will be robbed of radical prostatectomy because of that.

The inverse, I am very worried about a woman who gets this test for breast cancer and is told you do not have node-positive breast cancer, and, in reality, she does, and she ends up relapsing and dying from her breast cancer in 5 or 6 years from now.

With the mathematics that was presented here, I can guarantee you that is going to happen.

I just want to say that and I want to say,

yeah, we definitely need something that helps us to discern node positivity from node negativity. I like what I have seen here, but I think we need like 10 times as many patients as we currently have.

The next question I have for the FDA is am I allowed to consider the New England Journal data, which is not auditable and which the company has not turned over to you?

DR. MARTINO: Could we get an answer from the FDA on that?

DR. HOUN: It was submitted to the application with the right of reference, however, we have not been able to get any source documents, so we do not consider it a study that would support marketing.

You can give us your opinion of it, but it does not meet Federal requirements for a study.

DR. BRAWLEY: Thank you.

DR. MARTINO: Dr. Smetherman.

DR. SMETHERMAN: With respect to breast cancer, and Dr. Giuliano can probably speak to this

with even more authority than I, I think we have kind of almost moved past this level with sentinel lymph node.

We are not really looking at the sentinel nodes with just H and E staining, we are looking at them with immunohistochemistry. It is certainly as, you know, the sponsor pointed out, 61 percent of patients with a sentinel node only positive will have additional positive nodes, but I don't think they are suggesting that having this test, even if it were negative, would obviate the need for them to have the sentinel lymph node dissection anyway.

So, I think at least in what we are commonly doing on a day-to-day basis in breast imaging and breast surgery, this probably wouldn't really be that relevant.

DR. MARTINO: Yes.

DR. BUKOWSKI: I listened to Dr. Brawley and I must say I agree that the data we heard today just there is not enough information on the various patient groups to be convincing that, in prostate cancer, for example, this will be a useful test in

terms of the auditable data that were reviewed.

I am concerned that let's say we approve the application, as this material enters the use by individuals, there will not be proof of a positive node or a negative node, one will just accept the radiologic view of that saying it is positive or negative as we have heard.

The specificity and the accuracy doesn't sound like that would be supported by what we have heard today, so I am somewhat concerned by the number of patients that were included in the small subset. I just don't think there are enough prostate cancer patients, for example, to support utility in that particular setting.

DR. MARTINO: The problem that I have really are many with this. Do I think that this identifies certain lymph nodes that are not appreciated in other ways? I think they have convinced at least me that yep, that's true.

Is the value of this in people who have a node that is greater than 10 mm, where others would already have identified it? I am not sure that

that is the right place.

Is it really something that is of value in someone whose lymph node measures less than that, where other modalities might miss it? I am not sure they have convinced me how good they are in that setting.

So, I am actually very hopeful of this modality. I have to say that it does have some value in my mind. I am just struggling with am I sure enough of what its value is, to what degree can I trust the information that comes from it, and in whom can I trust it, where does it do nothing other than just confirm something I already knew, where does it allow me to avoid doing a surgery, where does it guide me to a lymph node that maybe I should do a surgery on.

There are just so many questions that I just, in my mind, cannot answer from the amount of data that has been presented, yet, I am intrigued that there is something here if only I could be sure of what that something was.

So, I am struggling with this whole

concept as to how trustworthy is the data at this point in time and how do I really use it clinically, because ultimately, if it can't be used clinically, in a manner that I understand, my guess is that everyone else will have the same problem.

The charge that this committee has is not just to sort of judge whether something is interesting. Lots of things are interesting, lots of things have some value. What this committee is charged with is giving an opinion as to whether, with the data that exists now, we are ready to basically say anyone out there should have this test available to them and the results of it should be then used for clinical judgment.

I am struggling with that major leap of faith, but I can't sort of lose track of what our real job is here.

Dr. Amendola, you are up next.

DR. AMENDOLA: Let me tell you I am a practicing radiologist with a special interest in GU radiology. Prostate cancer, as you probably know, is one of the most controversial cancers

regarding therapy today. One of the key reasons for this is that we don't have a good method of staging this tumor especially one of the problems is staging a lymph node, which is a key element for management of these patients.

There is another agent which is being used, which is another imaging modality is PET scanning, which happens to be not as good in the pelvis as in other areas of the body because of technical reasons.

I agree that the data that was presented was not completely convincing from a statistical standpoint, but I think that given the status of our poor accuracy with the current imaging methods that we have to image lymph nodes that are diseased in patients with prostate cancer, I think that taking the risk-benefit ratio, there is a group of patients with prostate cancer would be highly beneficial to use this modality.

If we could save some patients from unnecessary surgery or radical radiation, I think that this would be a very good thing to do. Thank

you.

DR. MARTINO: Dr. Levine.

DR. LEVINE: It seems to me that there is real potential for the agent, and my problem is that the indication that is being requested is not really based upon the data that would allow me to do that.

So, number one, the indication says all tumors, all comers basically, but the presentation is not dealing with all tumors, and somewhere in your documentation it excludes lymphoma as an example, but that is not stated on your indication, so the indication is too broad based upon the data presented.

Even the issue of newly diagnosed versus status post-radiation, you know, I see that it has been used in people who have had radiation before, and maybe that is valuable, but I don't know, and the indication doesn't state that or doesn't qualify that, so that would be another area that needs to be evaluated more carefully, studied more carefully.

The other indication, it seems to me, is in those tumors or those lymph nodes that are small, less than 5 mm, and if you now break down the data that exist into that group, you know, whatever the specific cancer is, and the newly diagnosed, and now less than 5 mm, there is so little data here that it is very frustrating.

I guess I would ask you to think of that and come back. Thank you.

DR. MARTINO: Dr. Hussain.

DR. HUSSAIN: So, I had the chance to hear the scientific presentation previously by the doctor from Mass. General who presented, and I think he did an excellent presentation again here today, and I guess in my mind, this technology is quite potentially promising, but I would underline potentially.

I don't believe the trials that have been shared with us, and the results of them, and certainly I think the designs were very flawed, I have to tell you that. I came in with more enthusiasm, and as I sat and listened more, my

enthusiasm went down.

I think the comments that were made about sparing people surgery or added treatment is a premature statement to be made. Staging gives you information. You use that information to make a decision.

I would point out that in today's standard, if there is a microscopic lymph node positivity, which is what you are talking about here, there are patients who are being operated on and offered additional therapy, so I don't think we need to play on the angle that if you have one node by the scan, that means you basically are to be doomed to no treatment or some hormone treatment that is not going to cure you. I think that is really the wrong strategy here.

The one thing about this from my perspective, I think what I would have liked to see is a well-characterized patient population where clinical and other predictors of outcome are incorporated and how this thing actually played in.

The other thing that I would point out is

the way you are asking for it would apply for people who have seen therapy and failed for assessment, so a guy who has had a radical prostatectomy or radiation therapy, and comes back with a rising PSA, is also covered under this umbrella, and I don't believe you showed us any data to say that this would be a reasonable thing to do.

I am not going to comment much about breast cancer, but I think the same thing applies. I would have loved to see a well done trial, a well characterized population, all the information out there, and the statistical assumptions to start with, what you are looking for, what did you expect, and I do reiterate that the template for the lymph node dissection is to me--I am an oncologist, not a surgeon--but it is important.

The questions that were asked from the surgeon before were very, very relevant, I think, and I think not having that information is a major flaw.

DR. MARTINO: Dr. Couch.

DR. COUCH: I routinely read my own scans before we decide in the tumor board what to do with my patients, and I view this as another source of information. I am going to scan all my patients to decide what their stage is and what the best treatment is.

The lack of evidence from that is always astounding to all of us. This, to me, seems a reasonably safe agent that could give you potentially more information. Would it determine alone what I do with our patients? No, it might make you think you would do a further testing or consider a node biopsy or a fine needle aspiration, but it is more information.

It is important even when we have people with disease to find out what the radiation reports will be, whether they are at high risk and therefore would qualify for chemotherapy. To me, the data was supportive of use in head and neck cancer patients.

These studies are difficult to do. I think they have done a good job, to understand that

the radiologists went to the operating room and looked at what nodal basins were being removed and analyzed was very reassuring to me.

So, I actually think that this is quite promising and the data, to me, is enough to approve this broad indication. I am a little confused, and I asked this of the FDA for the following reason. We order tests and we understand it is part of the treatment plan for the patient. It is not going to determine alone what I do with the patient.

You are asking this company to say we will approve this for a certain patient subtype that hadn't had radiation and chemotherapy, and then you want the company to come back again and again for each sub-subcategory?

DR. MARTINO: The FDA needs to answer that, please.

DR. HOUN: I think it depends on the drug and the indication and the disease being studied. A disease like ulcers, they get a treatment indication for acute ulcers. If you want to say you can maintain ulcer quiescence, you have to do

another study, a year-long study to demonstrate that.

So, there are disease conditions where to treat the level, the need for data on different stages of the disease, prevention of ulcers is totally different with NSAIDs. We do ask for different studies, and for diagnostic agents, we do have different types of indications.

They are seeking an indication for disease detection. They are not seeking an indication for patient management like to help you better stage. If that was the case, then, we would compare regular staging to this, and that would be the clinical trial.

So, they are asking for disease detection, and they are looking for cancer detection.

DR. COUCH: I think that is extraordinarily difficult. For instance, I am glad to see they excluded in their studies patients with head and neck cancer that had had previous radiation and chemotherapy. What happens to those lymph nodes is unknown, and we are having trouble

even with PET scans, which we think is probably the best imaging modality to understand which patients have residual disease in their lymph nodes.

So, I think it is a little bit different, and I think that that is decided upon with the understanding of the specificity and sensitivity and the clinical judgment.

DR. HOUN: If you give us advice that this is good for primary presentation and that further studies are needed for other presentations, we would like to hear that, or if like all comers are fine, we would like to hear that, as well.

DR. MARTINO: Dr. Mortimer.

DR. MORTIMER: As I think about decisionmaking in this process, I think about whether this test actually provides us information that will make me change therapy, and I guess I would reiterate what Dr. Hussain said in the prostate cancer setting. Given the sensitivity of PSA and the value of node dissection, I am not sure that it actually fulfills that criterion.

However, I would like to make a plea that

the more interesting data really isn't the head and neck population here who are underrepresented in the advocacy group for a variety of obvious reasons, and I think that data was actually the most interesting.

DR. MARTINO: Dr. Ownby.

DR. OWNBY: I have two interrelated concerns. One, as I understand the indication, and the FDA experts can correct me, this would be approved for all ages, and not a single group, and that would include children, and yet there is no child data in this.

My related concern is if you look at anaphylaxis and anaphylactoid reactions in large populations, young adults and teenagers seem to be at particularly higher risk, and the only age stratification of this data is the 65 and over, and I would certainly like to see some further stratification before considering that a very low incidence procedure while clinicians are clearly going to use it more in an advanced age population, I think this is a very broad approval request.

DR. MARTINO: Dr. Reaman.

DR. REAMAN: I would just follow with that. I think it is a very broad approval request and I think some of the comments that I have heard here, the real operative word in the review of this is promising. I think this is probably one of the most exciting agents we have had the opportunity to actually review in this committee, but unfortunately, the data presented to us was probably some of the least satisfactory from the standpoint of study design and conduct.

The FDA was criticized for making a low blow because of the mix of patients and the broad application. I would like to defend the FDA and I think including 10 patients or 15 or 20 patients with the three most common malignancies, and then asking for a broad indication is really inexcusable, whether it is in a primary diagnosis setting or in a previously treated setting.

I am concerned that if this were to be approved, that it would be used widely with no experience in the previously treated setting, in

the setting of follow-up, and in the setting of pediatric cancer.

Most patients or most children with cancer are diagnosed with disseminated disease, and the question of nodal metastasis is a very common issue. I think the fact that this hasn't been tested and the likely incidence of hypersensitivity reactions is a major concern.

DR. MARTINO: Dr. Brawley.

DR. BRAWLEY: Thank you. Dr. Reaman, I so agree with everything you just said. I really wanted to vote for this drug today, however, it is just not proven, it is just not proven with the data in front of us.

I don't want to get into a lecture on screening and epidemiology for the clinicians who don't normally get involved in this, but I will say for a diagnostic procedure, you typically want very high specificity, 95 percent or higher. This is specificity which is much lower than that, and that lower specificity means that the decisions that you make, you really have very little confidence in the

decisions that you are going to be making with that low specificity.

Now, one way that you can increase specificity is to enrich the patient population that actually has the disease, to use other clinical indicators, such that you are only using the test on people who are very highly likely to have the disease.

They tried to do that, and it is very fair. That is what I would call a fair selection bias. It would be not appropriate to do this test on somebody who you didn't know have cancer already, for example.

So, using clinical methods to increase or enrich the odds that you are going to find disease is totally fair, but even when they did that, the specificity is less than 90 percent in most instances.

I would concur that where we actually do have the best evidence of efficacy--and I actually split out efficacy versus effectiveness, they are different things--is in head and neck cancer.

DR. MARTINO: Dr. Bradley.

DR. BRADLEY: I am a practicing radiologist that has been doing MRI for 26 years. We often make decisions based on imperfect data, any of the clinicians in the room know that. What I have seen, I believe in. If it is approved for one set of cancers, the clinicians in this room will probably use it for all sets of cancers even though it is not in the package insert. We do that all the time.

But I would like to speak to the specificity and specifically to reducing the false negative. If they get a false positive, they get a biopsy. If they get a false negative, they die of their cancer.

There are technologies coming down the pike, in fact, many of them are on their way right now that are definitely going to increase the specificity of this agent. This is a magnetic susceptibility agent, turns things dark in a higher magnetic field.

I spoke earlier about why did you include

a 0.2T, well, the major market right now is 3 Tessler. Standard high field has been 1.5. We just ordered eight 3T's at UCSD. There is a larger market for 3 Tessler MR than there is for all of the low-field magnets now. 3 Tessler will be much more sensitive than 1.5 Tessler using the same technique for the same concentration. So, I would imagine the false negatives would reduce on that basis.

I also mentioned, I asked the authors of the New England Journal article how did they get exactly the same slice thickness. Well, there is a technology that is available in the brain called auto-align which gives you exactly the same position in the brain.

When I spoke to the inventor of that technique, could it be applied to the body, he said yes, it hasn't been yet, but it could be. So, now you have got exactly the same node pre and post, in exactly the same position, on a higher field scanner, using more sensitive techniques, I am sure that the false negative rate will be reduced and

the specificity will increase.

DR. BRAWLEY: Can I just say if I were presented that data, I would happily vote for this drug to be approved, but I haven't been presented with that data.

DR. MARTINO: Dr. Perry.

DR. PERRY: First, let me apologize to Dr. Li. I think I misinterpreted the sponsor's indication and I apologize to you and the FDA if my comments offended anyone. It was certainly not intended. I intend to rouse some rabble, but not unnecessarily.

Secondly, I am impressed by the safety of the agent. I don't have any particular concerns about that. I don't think there is anything you can inject into somebody intravenously that doesn't have some problems, and I think with the appropriate premedication and precautions, the drug is safe.

I am not yet convinced that it's effective and I am not yet convinced that it's effective for all the tumor types that it would conceivably be

used for, and at the moment I am inclined not to vote for it.

DR. MARTINO: Mr. Kazmierczak, please.

MR. KAZMIERCZAK: Yes. As I pointed out, I am a patient consultant to the FDA for prostate cancer. I was diagnosed back in '98 or '99, and at the time I had an MRI, which was negative, and I am not sure if I had had the Combidex-enhanced MRI that it would have changed the fact that I had a radical prostatectomy, I am not convinced it wouldn't have showed a negative result. I am not sure that the accuracy is such that it would have changed the therapy that I eventually elected.

I do agree with some of my friends up here that the more information you have on risk and benefit, the better the patient feels about the decisions that he makes. I found out a long time ago that I don't let doctors make decisions for me anymore, I try to work with them to make the decision.

It turns out even after my radical, my cancer was not confined to the prostate, it had

seeped into the seminal vesicle, and I am not sure that Combidex would have found that out. So, essentially, I have had a rising PSA, went on to adjuvant treatment with radiation.

I still have a rising PSA, so I got myself a Viadur implant, and I am not sure that any of these therapies that I went through, and I probably have a disease that really attacks me very badly, so I am probably going to die of this disease, and I am not sure there is anything available other than one of these wonderful clinical trials for me at this point.

That said, when I read this information, I was really hoping I could vote for this, but the more I thought about it, the more I wondered whether or not it would have made any difference to me in terms of the decisions that were made. That is my perspective. Thank you.

DR. MARTINO: Dr. Reaman.

DR. REAMAN: It was answered, thanks.

DR. MARTINO: Please.

DR. DYKEWICZ: To address a few issues

about safety, I do agree that the safety of the agent is within the realm of consideration for standard clinical practice. It is a question, of course, of always risk versus benefit.

The risk of this agent, I think is probably not that significantly greater than radiocontrast media, although it may be. We still are looking at relatively low numbers of patients.

I would say looking at it from an allergy perspective, although the radiocontrast media is certainly a relevant analogous situation, iron dextran may be a more direct analogous comparison, and there, of course, the reaction rate is somewhat higher than with radiocontrast media.

Unfortunately, if we look at strategies to reduce iron dextran reactions, nothing has really been held to large-scale trials. There are case reports about medication pretreatment as used in radiocontrast media to reduce the risk, but I am not clear that that would necessarily enhance the safety.

That being said, we do know from

radiocontrast media, which is analogous in the sense that this is most likely a non-IGE-mediated anaphylactoid reaction, we do know that medication pretreatment can significantly reduce the reaction rate.

Now, this also, though, gets at the point about what the type of medication pretreatment should be. When you look at radiocontrast pretreatment regimens that have been used, the best data for protection is where corticosteroids are given well in advance of the administration of the agent, for instance, a regimen that would give steroids 13 hours before or 7 hours before or 1 hour before, and not just, if you will, on call to the Radiology suite.

I am kind of really troubled by the fact of looking at, if you will, the standard of care for treatment of patients in Radiology administration areas in terms of what is done to, number one, pre-treat patients who may be at increased risk, and, number two, how to treat it.

I am not sure if there is good recognition

out there that you need to give steroids well in advance of administration in order to significantly reduce the risk.

I am pretty sure that there is a lack of awareness about when epinephrine should be appropriately used. I think this is a situation where evidence-based medicine and the standard of care are not meeting.

We now know that, for instance, with epinephrine, it should be given IM rather that sub-Q to try to get more rapid administration, and to summarize all these musings, if you will, I would say that it would be reasonable to try to reduce the risk of a reaction by using a medication pretreatment regimen that has been demonstrated to be effective in radiocontrast media.

Whether the company would be held to do that as part of a label indication, I think depends on whether you demonstrate good efficacy. I think my sense about this is head and neck cancer has been demonstrated to be a scenario in which this agent would be of value, and if you are looking at

a risk-benefit assessment, you could make a case for approving the drug.

But if we are looking at in general, the broader area of oncology, and having a very general label for all types of cancer, with an agent that maybe has a significant reaction rate risk of 1 to 2 percent, I think that gives me real pause for concern.

DR. MARTINO: Dr. Amendola, did you have a question?

DR. AMENDOLA: Regarding the question of the value of pre-medication, this is well recommended in the literature that you can decrease the rate of reactions by giving them the patient pre-medication with steroids especially for iodinated contrasts. I am not aware of any literature regarding this type of contrast. I have another comment.

There is currently an FDA-approved MR contrast material which is very similar to this one. It is called Feldex [ph], which is also an ultra-small, USPI, it is called. To my knowledge,

we use this fairly often, and we have not had any serious reaction and, to my knowledge, there has been no deaths related to Feldex, but maybe some other members of the panel have more experience with this.

DR. MARTINO: Dr. Hussain.

DR. HUSSAIN: I have a question to the FDA, Dr. Li, or any of the team. When the sponsor, I believe, or yourself mentioned that they sat down to talk to you about the design of the trial, what was the advice, and what was the spirit in which the trial was designed, was that designed for an indication approval?

DR. HOUN: I think that it has been a course over the years that we have worked with the sponsor, and I do have to say that their attempt to get the correlation between images and pathology, as you can tell as Dr. Anzai described it, is very difficult, and they did a very good attempt to try to do that.

So, we did look at their proposals, we provided comments. They revised according to our

comments. I think our goal was to ensure that pathology was obtained for these nodes.

I think your comment and the committee's comments what were other factors that might influence the actual surgical field, and were they well described, unless the sponsor has more information, I don't believe we were discussing those specific criteria.

DR. HUSSAIN: Did you tell them, for example, that you needed to have that many patients of that tumor because one of the critique regarding their request for the indication, that this is a blanket, and they did not address different tumor types, was that discussed with them in advance, that unless you come in with that number of patients with that tumor type, I mean in all fairness to them, if they listened to what you told them, and now it's not fair to them because they did exactly what they were told, and they come back and now they are told that is not good enough.

I guess what I am trying to find out what was the advice of the FDA in the first place.

DR. LI: I will try to give my answers. The interaction has been going on for six years. A lot of people give initial comment, may not be here anymore, but when we look at the record, you look at the original patient population is 181 and 162, and I don't think the sponsor anticipated, as we never anticipated, that so many patients was dropped from the study, was not able to do a primary analysis.

So, if all the patients was included, that may provide some--I mean I couldn't speak right now what the data might be, but will probably provide more assurance for us. This is one thing I don't think the sponsor realized at the design stage that so many patients--we didn't realize that either.

Also, I just make a point that there is another issue that both sides never realized is that pre-contrast MR sensitivity and specificity is a moving target. You see from a U.S. trial they made it from primary analysis, but from European trial, they never it. This is an issue that the sponsor and us never realized at the beginning, but

what I want to say is Agency really showed the maximum, at least showed the maximum flexibility, say if you really stay on the original design, the original design said you have to have two trials.

Each trial, your sensitivity post have to beat pre. That is basically statistical design. In the U.S. trial, they meet that design, they are able to show improved sensitivity, but in the European trial, they failed the sensitivity.

So, if you just take at face value, it's a failed trial, however, when we realized the reason they failed the trial, it is because they only included large size in the European trial. That makes the sensitivity so high, no way they can beat it.

So, we say let's go back, let's come back, look at more evidence, look at what's really the clinical question whether we can take a look at data to see whether it's clinical value.

So, that's why you see the analysis by subgroup. That was not original plan, that's true. The sponsor, what they said that's true, that's not

original plan, but when first primary analysis failed by the face value, when we started looking, by its group, by those things of value there, then, you see that this group is seen by size, by tumor, that makes people starting to realize wait a minute, what assumption we are having right now and whether we should approve it for broad indication.

That is why we come here, ask for your advice, to guide us how to handle the situation over here. I hope I answered your question.

DR. MARTINO: Dr. Bradley.

DR. BRADLEY: I have a couple of questions related to our relative lack of data, particularly for the wider indication. As a radiologist, I assume that all lymph nodes filter lymph and, in this case, Combidex, the same way.

Does anybody know that lymphoma, for example, would invade a lymph node in a different way? I know that they didn't get lymph node data, but they said it was because they had trouble getting pathology, so that is one question.

Another question for Gene, they missed

your seminal vesicles. Did you have an optimal MRI with intrarectal coil and the whole bit?

MR. KAZMIERCZAK: I believe I did.

DR. BRADLEY: You would know.

MR. KAZMIERCZAK: I believe I did, but I am like the statisticians, I am 85 to 90 percent sure.

DR. MARTINO: At this point, are there any final comments? Otherwise, I will bring the question to a vote.

Seeing no other hands raised, i will now call you to a vote, and we will start on my right with Dr. Couch, and as you state your vote, which is a yes or a no, I need you to state your name first for the record, please.

The question is do the data demonstrate that Combidex is safe and effective for marketing approval based on the sponsor's proposed indication.

DR. COUCH: Marion Couch. Yes.

DR. SMETHERMAN: Dana Smetherman. No.

DR. AMENDOLA: Marco Amendola. Yes.

DR. BRADLEY: Bill Bradley. Yes.

DR. GIULIANO: Armando Giuliano. No.

DR. DYKEWICZ: Dykewicz. No.

DR. OWNBY: Ownby. No.

DR. MORTIMER: Mortimer. No.

DR. PERRY: Michael Perry. No.

DR. HUSSAIN: Hussain. No.

DR. MARTINO: Martino. No.

DR. REAMAN: Reaman. No.

DR. RODRIGUEZ: Rodriguez. No.

DR. LEVINE: Levine. No.

MS. HAYLOCK: Haylock. No.

DR. DOROSHOW: Doroshow. Yes.

DR. BRAWLEY: Brawley. No.

DR. BUKOWSKI: Bukowski. No.

MR. KAZMIERCZAK: Kazmierczak. No.

DR. MARTINO: And our tally? There are 15 No's and 4 Yes's.

That is the end of our meeting. I thank you all for participating. Are there any additional questions from the FDA before I release the group?

Okay. There are no questions for the FDA. At this point, I will remind you that the next meeting begins at exactly 12:45 in this room. Thank you.

[Whereupon, at 11:58 a.m., the proceedings were recessed, to be resumed at 12:45 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:03 p.m.]

Call to Order and Introductions

DR. HUSSAIN: Ladies and gentlemen, if you don't mind taking your seats, please. We are going to try to start the afternoon session.

My name is Maha Hussain from the University of Michigan. I want to welcome you all to the afternoon session. The session will specifically deal with potential alternative endpoints to design trials for prostate cancer specifically with the intent of expediting the approval process of agents in this particular disease.

We will start with the introductions. I will begin with the FDA on my left. Dr. Williams.

DR. WILLIAMS: Grant Williams, FDA.

DR. KEEGAN: Patricia Keegan, FDA.

DR. SRIDHARA: Rajeshwari Sridhara, FDA.

DR. SHAMES: Dan Shames, FDA.

DR. BROSS: Peter Bross, FDA.

MR. MANN: Bhupinder Mann, FDA.

MR. KAZMIERCZAK: Eugene Kazmierczak, Patient Consultant, Prostate Cancer.

DR. BUKOWSKI: Ron Bukowski, Cleveland Clinic.

DR. BRAWLEY: Otis Brawley, Emory University.

DR. DOROSHOW: Jim Doroshow, NCI.

MS. HAYLOCK: Pam Haylock, Consumer Representative.

DR. LEVINE: Alexandra Levine, University of Southern California.

DR. RODRIGUEZ: Maria Rodriguez, M.D. Anderson Cancer Center.

DR. REAMAN: Gregory Reaman, George Washington University.

DR. HUSSAIN: Again, Maha Hussain, University of Michigan.

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

DR. MARTINO: Silvana Martino, Medical Oncology, Cancer Institute Medical Group, Santa Monica.

DR. PERRY: Michael Perry, Ellis Fischel Cancer Institute, University of Missouri.

DR. MORTIMER: Joanne Mortimer, Moores UCSD Cancer Center.

DR. GRILLO-LOPEZ: Antonio Grillo-Lopez. I am a hematologist/oncologist, a five-year cancer survivor this month, and the industry representative.

DR. SCHER: Howard Scher, Memorial Sloan-Kettering Cancer Center.

DR. D'AGOSTINO: Ralph D'Agostino, Boston University.

DR. D'AMICO: Anthony D'Amico, Dana Farber Cancer Institute.

DR. McSHANE: Lisa McShane, NCI.

DR. SANDLER: Howard Sandler, Radiation Oncology, University of Michigan.

DR. KLEIN: Eric Klein, Cleveland Clinic.

DR. DeGRUTTOLA: Victor DeGruttola, Harvard School of Public Health.

DR. ANDRIOLE: Jerry Andriole, Washington University in St. Louis.

DR. EISENBERGER: Mario Eisenberger, Medical Oncology, Johns Hopkins.

DR. RAGHAVAN: Derek Raghavan, Cleveland Clinic, Taussig Cancer Center.

DR. PAZDUR: Richard Pazdur, FDA.

DR. HUSSAIN: I would like to introduce Johanna Clifford to read the Conflict of Interest statement.

Conflict of Interest Statement

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

Based on the agenda it has been determined that the topics of today's meeting are issues of broad applicability and there are no products being approved.

Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All special government employees have been screened for their financial interests as they may apply to the general topics at hand to determine if any conflict of interest existed. The Agency has reviewed the agenda and all relevant financial interests reported by the meeting participants.

The Food and Drug Administration has granted matters waivers to the special government employees participating in this meeting who require a waiver under Title 18, United States Code Section 208.

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

Because general topics may impact so many entities, it is all not practical to recite all potential conflicts of interest as they apply to each member, consultant, and guest speaker.

The FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussions before the

committee, these potential conflicts are mitigated.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Antonio Grillo-Lopez is participating in this meeting as an acting industry representative acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Disease Research.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participant 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 make a couple of comments

before Dr. Pazdur begins his presentation. We have several invited experts to discuss different aspects of PSA and other endpoints as it relates to prostate cancer.

The intent with this afternoon's session is not so much to come up with a specific endpoint to address necessarily, but rather a task list of what perhaps is needed to begin to develop different endpoints for evaluation of drugs in an expedited manner in prostate cancer, so I would like us to, as much as possible, focus on that issue, and not get hung up on little details that may not be serving the purpose as a whole.

Without further delay, I would like to introduce Dr. Richard Pazdur, the Director of Division of Oncology Drug Products, as the first speaker.

Opening Remarks

DR. PAZDUR: Thanks, Maha.

I just have some introductory comments to go over the process that we are addressing here today. As you know, part of one of the big

initiatives that the Division of Oncology and Oncology, in general, at the FDA, has been to perform a review of different endpoints diseases, and these endpoints are the approval endpoints that we would use for approval of new molecular entities and also supplemental NDAs.

This is a process that we have tried to integrate into the greater oncology community and, hence, before we have ODAC meetings on specific diseases to discuss endpoints, we usually have a workshop, and we had a workshop on prostate cancer. It has been almost about a year ago, I think, where we had a workshop in Bethesda, held in conjunction with ASCO and AECR.

The purpose of this meeting was really to explore areas and controversies of endpoints, and I think one of the most controversial area obviously was the optimal use of PSA, how to use it, when to use it, where to use it, and I think a lot of discussion that we will have today will center on the PSA issue.

As Maha stated, I think one of our goals

is not to achieve direct consensus here, but to raise issues. If there is consensus, let us hear it, and we will be happy to take it into consideration.

One of the things that I was most impressed about as far as attending the workshop that we held was the controversial nature of PSA and endpoint for prostate drug development, and I think we should be aware that there can be agreements or disagreements, but ultimately, at one time or another we are going to have to come to some decision on the use of biomarkers in prostate cancer.

So, I am not trying to discourage discussion on this or lack of consensus, but I think we have to be realistic that there are many controversies that exist today in the use of PSA.

If I take a look at the other diseases that we have held workshops on, for example, colon cancer and lung cancer, I would have to say that this has been the most difficult area to review, and the battling of different people and different

ideas regarding PSA has been one that has necessitated the Division actually to have separate meetings and separate discussions with people in the academic community after the ODAC meeting.

Here again, I think the one thing that was clear is that this is a controversial area that we need to bring some plans on how to further develop this.

Hence, therefore, we have the program that is outlined in your sheet that has been provided to you. The first talk will be by Dr. Bhupinder Mann, who will go over our past regulatory approvals for drugs. That is what we have done.

Then, we have asked Dr. Derek Raghavan, who was one of the Co-Chairs of the ASCO-AACR meeting, to basically try to summarize the highlights of that ASCO-AACR meeting, and his talked is entitled "Towards a Consensus in Measuring Outcomes in New Agents for Prostate Cancer.

The third talk is one that will be given by the NCI, and it is the NCI Prostate Cancer

Treatment Trial Portfolio. I was interested in bringing this issue up because I think if we do discuss endpoints, there has to be a discussion of prospective evaluation of these endpoints, and we have to have an idea what the NCI is doing as far as supporting prostate cancer research and how we can utilize those trials to embed endpoints and to look at them in a prospective fashion. Hence, we have asked the NCI to please provide data, not data, but a description of ongoing research that they have.

The last two talks, given by Dr. Howard Scher and Anthony D'Amico, basically stemmed out of our AACR and ASCO symposium, and is somewhat an exploration of issues that were explored during those workshops.

Howard will give a talk entitled "Toward an Endpoint for Accelerated Approval for Clinical Trials in Hormone Refractory Prostate Cancer," and then Dr. D'Amico, Anthony D'Amico will end by discussing clinical trial designs for selected patients with a rising PSA following primary

therapy.

I want to emphasize we are not here to bury PSA, we are not here to praise PSA. We are here basically to have a discussion of the existing data that supports its use. Any endpoint that we have for drug approval has to be credible.

I am not asking for perfection here with any endpoint, and as you realize, we have used many endpoints that are not true surrogates. For example, in our accelerated approval program, we ask for surrogates that are reasonably likely to predict clinical benefit, but we have to have some basic comfort, some basic understanding of that endpoint.

That endpoint has to have credibility and some acceptance, not only by the FDA, but by the greater oncology world, and that includes you people as investigators and also patients.

With that ado, I will turn over the program to Dr. Hussain.

DR. HUSSAIN: Thank you, Dr. Pazdur.

Dr. Temple, would you please for the

record state your name.

DR. TEMPLE: Robert Temple. I am the OD-I Director, Office Director.

DR. HUSSAIN: Thank you.

Our next speaker is Dr. Bhupinder Mann, who is a medical officer, Division of Oncology Drug Products, and the discussion will be regarding a regulatory perspective of endpoints to measure safety and efficacy of drugs in the setting of hormone refractory prostate cancer.

A Regulatory Perspective of Endpoints to Measure Safety and Efficacy of Drugs: Hormone Refractory Prostate Cancer

DR. MANN: Good afternoon. I am going to first present a review of the endpoints which have been used during the past few years in approval of drugs for treatment of advanced hormone refractive prostate cancer.

I have focused specifically on these approvals as these are illustrative of the underlying regulations. Later, I will also summarize some of the difficulties which are

encountered in reliably measuring safety and efficacy of treatments in prostate cancer, reviews of both the traditional and the innovative endpoints.

Approval of a new drug requires substantial evidence of effectiveness derived from adequate and well-controlled clinical investigations.

Before 1992, endpoints used for drug approval were required to represent clinical benefit. Some of the endpoints were direct measures of clinical benefit, for example, improvement in survival or improvement of disease symptoms. Others were accepted surrogates for clinical benefit, for example, durable complete responses in acute leukemia.

Since 1992, accelerated approval regulations have allowed the use of surrogate endpoints that are reasonably likely to predict clinical benefit. Accelerated approval may be used when a new drug would provide benefit over available therapy. Accelerated approval also comes

with a requirement to do post-approval studies to confirm that the drug does provide clinical benefit.

During the last 10 years, three drugs were approved for treatment of advanced hormone refractory prostate cancer. Each of these three approvals was based on clinical benefit endpoints. None of these drugs was approved under the accelerated approval regulations.

Most recent of these approvals, that of docetaxel in 2004, was based on demonstration of improvement in the overall survival. Overall survival remains one of the most meaningful endpoints in controlled clinical trials in cancer. It reflects both the safety and efficacy of a treatment.

It is an obvious direct measure of efficacy and a longer overall survival, also provides a reassuring measure of safety. A therapy with significant toxicity and possible mortality of its own is unlikely to result in a net survival benefit.

Efficacy of docetaxel, in combination with prednisone was demonstrated in a well-controlled clinical trial by a significant prolongation in overall survival.

In the pivotal trial TAX-327, two different schedules of docetaxel administration, 3 weekly and weekly, were compared to a control arm of mitoxantrone. Each of the 3 arms included prednisone.

Cumulative dose of docetaxel administration in the 2 study arms was the same at 750 mg/sqM.

1,006 patients are enrolled in this trial. Primary efficacy endpoint was overall survival. This was defined as time from randomization to death from any cause.

Overall survival was significantly superior to the docetaxel given every 3 week arm compared to the control arm mitoxantrone, and the results of every 3 week comparative arms are summarized in this table.

Median overall survival was 18.9 months

for docetaxel and 16.5 months for mitoxantrone. This was statistically significant.

FDA has accepted endpoints based on measures of patient symptoms and other non-survival indices of disease morbidity. Marketing approvals for mitoxantrone and zoledronic acid were based on non-survival endpoints.

Mitoxantrone, in combination with prednisone, was approved in November of 1996. It was approved for initial chemotherapy for treatment of patients with pain-related to advanced hormone refractory prostate cancer.

Its efficacy was shown in an open label, Phase III controlled clinical trial, 161 symptomatic patients are enrolled. Endpoint used was palliative response. This endpoint was prospectively defined. It consisted of a 2-point improvement on a 6-point pain intensity scale, accompanied by a stable analgesic score and duration of improvement lasting at least 6 weeks.

A palliative response was seen in 29 percent of the patients who received mitoxantrone

compared to 12 percent in the control arm. Median duration of this palliative response was longer for mitoxantrone at 229 days compared to 53. Median time to disease progression was significantly longer, 301 days compared to 133 days, however, this trial of 161 patients did not demonstrate a statistically significant difference in survival between the two arms. PSA decrease of 75 percent or greater was seen in a significantly high number of patients in the mitoxantrone arm.

Zoledronic acid is a bisphosphonate. In 2003, it was approved for treatment of patients with progressive bone metastases from prostate cancer.

Endpoints used in that trial was a composite endpoint of several skeletal-related events. A composite endpoint can be useful when disease manifestations are diverse. It can increase the power of a study.

Previously, this endpoint had been used to measure efficacy of pamidronate for lytic bone disease in multiple myeloma and breast cancer.

Several prospectively defined skeletal events were included in this composite endpoint: pathological bone fractures, spinal cord compression, and surgery or radiation therapy to bones to treat a fracture, to stabilize an impending fracture, to prevent or treat a spinal cord compression, or for pain relief.

A change in the antineoplastic therapy due to increased pain was an added event specifically for this prostate cancer trial.

Efficacy was demonstrated in a placebo-controlled, double-blind trial of 643 patients. There was an 11 person absolute decrease in the proportion of the patients with at least 1 SRE favoring zoledronic acid. Another measure of efficacy was an increase in the median time to first skeletally-related event. This was 321 days for the control and this had not been reached for the zoledronic acid arm.

Now, I will briefly present the difficulties encountered in evaluating treatments of prostate cancer. These issues will be covered in

depth by Dr. Raghavan.

In general, difficulties encountered in evaluating treatments of prostate cancer stem from several factors. These relate to the characteristics of the disease itself, characteristics of the patient population, and the prevalent clinical practices.

One disease factor that makes it difficult to evaluate treatment is the heterogeneous natural history of both the advanced and the early stage prostate cancer. Disease course is highly variable with diverse clinical manifestations.

At least until recently, that is to say until docetaxel approval, use of traditional endpoints, for example, overall survival in evaluation of treatment efficacy had been of very limited utility.

In this disease, on one extreme in many patients a rising PSA may be the only sign of the advanced disease. These patients do not have any disease-related symptoms, their bone scans are negative, performance status and quality of life

are well preserved. Although the survival experience of these patients can vary, the vast majority have a relatively long survival.

On the other extreme, there are patients who have rapidly progressive disease, they have disease-related symptoms, their performance status is affected by their disease, quality of life is impaired, and their survival is shortened.

Clinical benefit of treatment is now well established for these patients.

Two characteristics of the patient population which make it difficult to evaluate treatments for advanced prostate cancer are the advanced patient age and comorbid conditions. Whenever you measure survival, and a large number of trial participants have a disease with a long natural history, the observed results are confounded by competing causes of mortality, and interpretation of the observed results can become difficult.

Thus, the advanced age of the vast majority of the patients with prostate cancer and

comorbid conditions they may have at that age, they can make conduct of a clinical trial and interpretation of the results difficult.

These patient characteristics are often cited as an explanation for the inability to show clinical benefit in terms of overall survival prolongation both in prostate cancer and other advanced cancers.

However, in 2004, investigators were able to show overall survival advantage for docetaxel in two different clinical trials even though they used slightly different regimens. One can argue that it was the lack of drugs with enough activity that it was difficult to demonstrate clinical benefit in terms of an improvement in overall survival.

Finally, prevalent clinical practices are a factor which lead to difficulties in evaluation of treatments for prostate cancer. Currently, in clinical practice, as well as during the conduct of clinical trials, treatment changes are frequently driven by changes in the PSA level, thus, many patients can go off study before any clinical

endpoint of disease progression is reached.

Subsequently, data on other endpoints of interest may not be collected at all. Collection of such data is necessary to eventually define clinical benefit from a treatment as well as to confirm the validity of a surrogate endpoint.

PSA-based endpoint may be acceptable surrogates for anti-tumor activity of a drug, for example, in a Phase II clinical trial. However, reliable use of PSA-based endpoints as surrogates for clinical benefit in Phase III controlled clinical trials when two treatments are being compared, it remains to be defined.

This needs to be explored further. A surrogate endpoint that is reasonably likely to predict a clinical benefit can be the basis of an accelerated approval. However, the new drug should provide an advantage over available therapy, and the clinical benefit needs to be confirmed subsequently.

Thanks for your attention and I would like to acknowledge the contribution of all these

individuals for this.

DR. HUSSAIN: Thank you, Dr. Mann. We will hold all questions until the final speaker, Dr. D'Amico, and then we will open up the floor for discussion.

Our next speaker is Dr. Derek Raghavan, who is Chairman of the Department of Hematology and Medical Oncology at the Cleveland Clinic Taussig Cancer Center. He will discuss Towards a Consensus in Measuring Outcomes in New Agents for Prostate Cancer.

Towards a Consensus in Measuring Outcomes in New Agents for Prostate Cancer

DR. RAGHAVAN: It is always a pleasure to follow Dr. Pazdur's introduction because, as you know, the FDA is characterized by scholars of Shakespeare, and I personally was relieved that he chose to quote from Julius Caesar rather than from Hamlet, because I thought he would have probably gone for the cheap shot of asking the question to pee or not to pee, but fortunately, he didn't.

So, my task is to discuss some of the

complexities that came out of the meeting in which our original plan was to try to achieve a consensus about what should be the new era of evaluating prostate cancer studies, and as Dr. Mann has said very elegantly, there are a number of confounding variables that make it difficult.

Probably the hardest thing is that prostate cancer spans such a broad spectrum, and it goes from a disease that unfortunately can kill people in less than a year to a disease that can be metastatic and which can co-exist in a patient for more than 10 years, and the key is to try to identify which variant of the disease one is dealing with.

As Dr. Mann mentioned, there are the additional confounding variables of the advanced age of the patients and the many symptoms of aging that go with them, and Dr. Eisenberger and I were just commiserating with each other that having worked together in this field for 30 years, we now have most of the symptoms that our patients have acquired, and it's a sad thing, and the point that

I make is to the best of my knowledge, both of us have normal PSAs, and yet we have aches and pains and sometimes failure to thrive and fatigue, so it can be really quite difficult to identify the specifics of the disease against the background of a well older patient.

Then, there is the phenomenon of death from competing risk, which happens in any of the studies that are relatively long.

Howard Scher made I think an important contribution and spent some time talking about this at our series of meetings of what he terms the states model and what many of us would simply identify as the staging approach to prostate cancer, and I think correctly Howard has made the point that there are many different scenarios that the FDA will need to address in quantifying drugs that are presented here.

There is the sort of conventional testing ground for new medications in prostate cancer, the patient with advanced conventional metastatic disease. When some of us started practicing the

management of prostate cancer, the typical patient would have a large volume of disease with narcotic-dependent pain, potentially pathological fractures, and that has changed over a period of time.

There is the question of whether one has had effective hormonal therapy, and with some of the newer regimens that are around, there are data that suggest that some of the newer drugs don't as effectively suppress hormones as some of the standards of care, and there are compliance issues and issues that relate to drug uptake.

Then, we are looking at earlier stage of disease when we are faced with using more advanced treatments. With the increasing microscope that is focused on prostate cancer and pressure from the community to deliver the goods, patients are looking to find relapse at an earlier stage, and physicians are being faced with the problem of sometimes treating disease that they can only measure biochemically, which certainly will have changed the situation, and that leads us to the

phenomenon of stage migration, which I will return to through this presentation - in brief, changes in imaging, changes in the use of PSA and other markers, and even a functional migration in that we are now tending to use quality of life parameters as another measure of outcome, so that the goalposts in a way have widened.

Normally, when I steal Howard Scher's slides, I apologize and act embarrassed, but my role is, in fact, to summarize discussions that we were involved in, so I steal these slides with absolutely no apology at all. There are only two, Howard, of yours, so I am not actually giving your talk for you, although I will do it perhaps a little more elegantly and with larger words.

So, I think an important point that Howard has demonstrated here is the concept of a continuum of disease from the initial prostatic evaluation through to advanced disease, and the reality is that a particular product can be used at multiple points through the course of the disease, and thus one would anticipate different types of outcome.

One has even the situation for the asymptomatic patient where one may decide to do nothing and simply watch the patient in the context of a slowly evolving disease, and that brings in the biggest problem.

At the moment, there is a vogue, an affection for stable disease as a rediscovered category. There are now a series of static drugs where the claim is that these drugs somehow influence the natural history of the disease by making it more stable than it was before the drugs are used, and that may be a very reasonable concept, but it is a concept that is somewhat alien to the standard practice of oncology, and what, in fact, is a cause of concern is that there may be the potential for misinterpretation of data when one has the phenomenon of stage migration, such that one is looking at stability of disease at an earlier phase in the natural history of the disease.

So, that is where the question of PSA as an initial endpoint and quality of life measurement

will come in.

Just to remind us all of the scenario and remembering that we have the world's expert on AIDS here, Dr. Alexandra Levine, who shared prostate cancer patients with me at USC, but just to remind her of the history that antedated her involvement into oncology, I would just like to remind you that the Nobel Prize for Medicine was awarded to Charles Huggins and Clarence Hodges, I think Hodges being the only urologist ever to win a Nobel Prize, and that was given for the demonstration of an ability to suppress the growth of prostate cancer in dogs.

The models that we used in the pre-1960s era were essentially much cruder, but were still a good reflection of the disease as we know it today. They just reflected a more advanced variant of the disease going to Howard's states model, the more advanced end game part of management.

Human studies at that time, as I mentioned, were characterized by patients with large tumor cell volumes and symptoms to go with them. Unfortunately, at the time, although they

were the best available, the endpoints that were measured were imprecise, they weren't structured ways of measuring the degree of improvement of pain.

We maybe correctly or maybe incorrectly said pain, yes or no. There was the acid phosphatase measurement, which was clearly an imprecise one that correlated occasionally, usually Monday, Wednesday, and Friday with disease outcomes, but Tuesdays, Thursdays, and Saturdays didn't, and Sunday was in the eyes of the Lord.

So, the reality of the situation was that we had markers that were unreliable and didn't correlate directly with tumor volume. So, ultimately, the one quantifiable endpoint came to be survival, and that stood the test of time.

Now, as physicians spent more time dealing with patients with varying stages of prostate cancer, they started to look for different surrogates of outcome, and it was in that period that the National Prostatic Cancer Project, one of probably the most underappreciated useful entities

that we have had in the U.S., actually did a lot of very important work, were able to start to model the concept of the variability of the different states, they just didn't call it that.

So, they identified the category of stable disease within prostate cancer, identified that there was a variant that evolved slowly, and then set about trying to structure what constituted stability and were there different levels of stability and could you influence stability in a meaningful way.

In other words, if a patient had absence of progression for 6 months, was that less good than absence of progression for 12 months, and the logical answer to that would be sure, provided the progression was being measured in an accurate way.

The whole situation became a little more complex with the very, very important identification by Ming Chu and his colleagues at Roswell Park of the entity prostate specific antigen, which has totally revolutionized the way we think about prostate cancer. The truth of the

matter is that it has allowed us to start to look at this disease in a subclinical way.

The problem is that this has had its own complexities, and as we have used PSA more and more, we have come to understand that there is the phenomenon of release, so sometimes PSA going up is good, and sometimes PSA going up is bad, and the problem has been that with the passage of time, our ability to quantify outcomes has been obfuscated by a lack of understanding of this molecule and its production.

Once again, in the 1970s to the 1990s, the availability of PSA led to stage migration and because it was being used for screening purposes, resulted in functional terms in a much higher level of awareness of the public of the entity of prostate cancer which heretofore had not really been a very well-known entity at all.

Bhupinder Mann has shown you this snapshot of the approvals, and this is simply to remind us of the parameters that we used for approval in the past.

Now, currently, there are a number of situations that bring pressure on all of us to try to come up with the goods, and which certainly led to some extent to the development of a series of meetings to try to structure our assessment of outcome of novel products, be they cytotoxic or cytostatic.

There is question that the microscope is on the community of patients and physicians who are involved with prostate cancer. There is a requirement for us to do better than we have done. This is a common entity, it is being diagnosed more frequently. It may even be developing into epidemic proportions.

It is not absolutely clear whether that is reservoir effect or a real finding, but what is absolutely clear is that in contrast to the United States, if we look at the Far East, in Singapore, in Hong Kong, in China, there is clearly an epidemic of prostate cancer and no one knows why.

It is clearly more than just doing PSA screening. It may have to do with lifestyle and

diet, it could be a whole bunch of things, but it is quite clear that prostate cancer incidence rates are increasing rapidly, so we are going to be faced worldwide with an epidemic of this disease and need to be ready for it.

Currently, there is a new era of stage migration. We now have the PET scan, which is being rationalized as useful for the diagnosis and management of advanced prostate cancer.

At the symposium that we held some months ago, Dr. Steve Larson from Memorial Sloan-Kettering gave a very erudite discussion of the new strategies of quantifying response using radionuclide bone scans, tomography, and the new tools, so this is again allowing us to look at both outcome migration and stage migration in a completely different way.

As you have heard mentioned, as I am going to talk about, and I am sure Howard will, as well, there is a refinement in the understanding of PSA response. So, at the present time, new endpoints are being presented.

Clearly, there is an increased refinement of measurement of quality of life, and I would like to talk about that, because I, in fact, am not a great believer at least in using the refinements of quality of life measurement as an index of acceptance today. I don't think we are ready for that.

The issue of absence of progression for some of the cytostatic agents I think is going to be perhaps the most controversial item that we will need to face today, and then the issue of having PSA, prostate specific membrane antigen, PSMA, and the whole concept of time-dependent fluxes.

There was a time when we simply said if it goes down, that's good, now we are starting to look at time points and trying to interpret what is a significant time point - is a 50 percent reduction at 3 months better than a 50 percent reduction at 2 months, and, if so, how much better and what does it mean.

So, ultimately, we have a whole series of different endpoints, and the key question I think

that we need to address today is should survival still be regarded as the standard, and if it isn't the ultimate test, because it is confounded by death from other causes, because it may be confounded by a series of salvage therapies, in other words, a new drug may work for a time and then depending on the pathway that the patient follows, again going back to the state's model, you may end up having different follow-on pathways of treatment.

If survival isn't an ultimate test, and we decide to bring in quality of life with some of the surrogates, will they lead us to new treatments that actually alter outcome.

The big concern about the screening debate today has been we are not still sure after many years of PSA screening, are we actually saving lives or are we just moving the diagnostic point.

So, one of the things that I think is a concept that most people who treat prostate cancer, be they surgeons, radiation oncologists, medical oncologists, or palliative care physicians,

whatever point in the disease, I think we would all recognize that for the different states of the disease, the aims are going to be different, and this is essentially taken again from Howard's presentation although it is not his slide, just identifying the different aims and outcomes that relate to each of the stages of the disease.

Clearly, the focus will change from when there is very little disease, trying to stop it from evolving into something that is life-threatening versus when there is advance to hormone refractory disease, then, actually feeling that you are playing what might be an end game and trying to prolong that for as long as possible.

So, clearly, acceptance of drug X for the patient who has PSA-only disease with no bone scan, no physical findings, no symptoms, the nature of what will influence the acceptance of that entity, the force must be different from what will influence the acceptance of an entity on your right, in other words, advanced hormone refractory disease that is symptomatic and which has the

potential to kill a patient in three to six months.

Again, for those of you who aren't familiar with prostate cancer, this gives you a sense of what a protein disease it is, and even today, in a high end clinical practice such as at Memorial Sloan-Kettering or M.D. Anderson or the Cleveland Clinic, or any of the places, Hopkins, that have major prostate cancer programs, people every day of the week will see patients who happen to come in, not knowing about prostate cancer and therefore having allowed the disease to get totally out of control with a whole series of constitutional features that can cause hemorrhage, that can cause pruritus, it can cause weight loss, it can cause symptoms related to the sites of metastatic involvement, back down to the patient who will come up after a radical prostatectomy or radical radiotherapy with a PSA that has gone from 0.05 to 0.1, so it is very difficult for the FDA to look at this, in my opinion, as a unit entity.

So, one of our tasks will be to try to give advice to ODAC about how to structure the way

of presenting a framing reference.

This is some work from Don Newling from the United Kingdom, and it is just illustrative of just how big an impact stage of presentation can have, so this was looking at a series of his Phase II trials where he looked at simple parameters that resulted in the presentation of patients, and as you can see, the median time from progression to death, for example, for just a PSA increase was dramatically different from the time frame for a patient who presented with a liver metastases.

Now, today, there is a new nuance that we understand, and that is that many patients who present with liver metastases don't actually have classical adenocarcinoma of the prostate.

Today, if you summarize the folks around this table who see prostate cancer and treat it, and ask the question what do you think about when a patient presents with liver metastases in isolation, everyone will tell you I think about neuroendocrine small cell variant carcinoma.

It may not be that, but it is almost

certain that many of the cases over the last 20 years, that have shown response in the liver with prostate cancer, have probably been of that variant. So, that is a novel entity and again relates to a histological migration with time.

So, one of the things that we need to deal with is the impact of earlier intervention and what it does to survival curves, so, for example, we have heard mention briefly of two pivotal studies that were reported in the New England Journal of Medicine earlier this year, one led by Dr. Eisenberger, who is here, and one from the Southwest Oncology Group and its friends, and the principal investigator of that was Daniel Petrylak, and I was involved in that publication myself.

So, this was a survival curve that was yawned at by the press. They looked at the figures. They said p value of 0.01, Taxotere better than mitoxantrone, big deal, and if you look at that survival curve, I think you have to accept that this is not a home run. It was the first or one of the first two trials that showed a survival

benefit for one drug over another, and that is important.

It was very similar if we go back 15 years in the history of breast cancer to the sort of figures that we saw in advanced breast cancer, that went on to help us develop therapeutic strategies of adjuvant care.

In fact, this type of study has led to the development, for example, of SWOG-9921, a randomized trial that looks at hormones plus or minus chemotherapy for patients with locally advanced prostate cancer, but accepting that it's an interesting paradigm, those curves are not very impressive to look at.

Just note that the number of total cases is 670 and keep that in mind.

Now, if you want to consider the surrogate outcomes, that is way more attractive, and this relates to the 50 percent PSA reduction that was identified, and blind Freddie could identify the difference on the left of docetaxel versus, on the right, mitoxantrone, and that is the stuff that

headlines are made of.

So, we decided that we would do some modeling in the Southwest Oncology Group, and this is work that was done by Catherine Tangen [ph], who is a lead biostatistician in the GU Committee, Genitourinary Cancer Committee, and she did some very interesting modeling where she looked at survival by a surrogate, which was 50 percent PSA reduction at 3 months, and that actually is quite impressive.

If you had treatment A versus treatment B, you would say home run, that's a really big difference. So, here, what we are identifying is that a surrogate outcome is actually reflective of an important endpoint, and if we make it a little more interesting, and we then put in the responses broken down for the type of treatment, you will see that again the key difference relates to surrogacy, but here is the problem.

Let's go back for a minute and add the numbers of risk, and what you will notice is that the number is 520 patients would had serial PSA

values, 520 out of nearly 700 cases, so what that means is that we have lost from the denominator a large number of cases.

The reason that is important, if you go back to here, is look at the number of deaths in that study, and the number of deaths, while clearly important, in absolute terms is not all that dramatic.

So, the point that I wanted to make in taking you through this circuitous argument is that we need to be extraordinarily careful when we leap to a new surrogate, if we don't set the framing reference of did we lose patients by using that surrogate and what happened to the patients that we lost that might have influenced the outcome, in that situation we need to be very careful before we set new standards.

So, my plea today is that we shouldn't be setting new standards. I think we should be identifying endpoints that require further study and that the FDA might be able to require in the trials that are presented to them. I think the FDA

has the potential to influence medical history here by making certain demands.

So, my view is we are not ready for prime time changes to outcome, but I think we are ready to look for new indicators of outcome.

Now, measurement of quality of life has been particular popular, and unfortunately, somehow one is cast in the role of being anti-patient if one says that one doesn't like quality of life measures as a finite indicator.

I hope that my clinical career hasn't suggested that I am anti-patient, because I see myself as a substantial patient advocate. I just don't happen to think that this set of measurement tools is ready for interpretation yet, and the reason, I have summarized here. There is difficulty of assessing response.

Within the stable category, we have a widening of the goalposts and the problem is that measures of quality of life, as I mentioned, as Dr. Eisenberger and I creak through our coffee and biscuits that he was kind enough to bring to my end

of the table, those measures of quality of life are confounded by the age and intercurrent problems of the patients.

They can relate to age, they can relate to therapy, they can relate to a whole bunch of things, and as we look at the data that are available to us, there is clearly a dichotomy between objective measurement, subjective measurement, and whatever in that frame of reference PSA constitutes, which is somewhere I guess in the middle, but closer to objective. I think the key problem is that the optimal technology has not yet been defined.

Now, what is good is that we have, in fact, begun to rationalize our approach to this. So, again, I want to be very clear that I am not opposed to developing the methodology. I just see it as still work in progress.

These are some of the patient reporting domains that will come up again and again in the different quality of life assessment schemes, and I am not going to read them, they are all provided in

the handouts that are available, but they relate to different ways of looking at a patient and asking the question how do you feel.

There are structured scores like the McGill Melzack, which involves looking at present pain intensity, and there it is an attempt to mathematize the assessment of outcome. The problem is it is not yet clear what is the best way of using this tool.

It allows for a 2-point reduction, which is the best type of reduction. Ideally, if you have a 2-point reduction on the McGill Melzack scale from 2 down to zero, that is a big win. But what is the impact if you happen to have a tough Anglo Saxon dockworker who has a high pain threshold and claims only to have one level of pain at the beginning and he goes to zero. Is that somehow less important, and the answer is we don't know.

What if there is no pain, but there are a whole series of bone metastases that are present, what is the impact of having no change in pain?

So, my point is simply that all the models that I have summarized up there address that dichotomy very poorly.

The problems include the impact of baseline variables, as I have said, we don't really know how to score them, we have got no good model for dealing with missing data, in other words, the patient who doesn't fill in one of these scales, is he too sick to fill it in, is he so well that he couldn't be bothered, is he not bright enough to, is he too busy? In other words, we don't know how to integrate that into our assessment of this endpoint.

The statistical analysis is another problem, do we look at absolutes, do we try to construct an area under the curve for the number of days spent in agony versus the number of days spent doing wonderful things.

We don't have a good mechanism, we don't even have a model, such as looking at receiver operating characteristic curves, which we use sometimes when we are not quite sure where a cut

point appears because we don't know how to define the cut points properly.

So, our confounding variables, to add up to that, is what the patient knows. We have tremendously educated patients, so you can have--and I am sure the physicians on the panel have seen this--a patient who comes in and you say how are you feeling, and he says great, and you say, well, I am glad because I have some bad news, your PSA just went up 50 points, and they walk out feeling horrible.

It is not that there is anything foolish in that, it's that knowledge of PSA is integrated into the model, and so it confounds our ability to assess it.

There are clearly differences in the way different racial groups and different societal groups address pain, death, dying, cancer, and our models don't allow for those differences of perception.

So, then the question is what does that leave us with, and I thought I would use an

illustration which was the one that Dr. Mann mentioned, of how mitoxantrone was approved.

Studies of mitoxantrone in the Phase II fashion dated back to about 1982-83. I think in Australia we did one of the very early ones where the assessment of quality of life was whether you could drink a beer. That didn't translate to the USA, but it was a pretty good endpoint as far as I was concerned.

More recently, Ian Tannock, who has one of the leaders in assessment of quality of life with the Canadians, did a randomized trial comparing mitoxantrone plus prednisone versus prednisone alone, a small number of patients, and the primary endpoint was palliation with a secondary endpoint being survival.

Now, this survival curve has been interpreted universally to show that mitoxantrone doesn't improve survival, and that is a fundamental misunderstanding of the design of the study, because in truth, this was a relatively small study, the p value, in fact, reflected a trend in

favor of mitoxantrone for survival, and the key issue was this study allowed crossover, and so it allowed a patient who was on prednisone, if he progressed, to cross over to mitoxantrone.

My interpretation of this study is that--and it has influenced my practice heavily--is there isn't necessarily a rush to run to chemotherapy in a patient if you have a relatively indolent pace of disease.

But what influenced the FDA, I think correctly, was this chart, which was an attempt to look at area under the curve for quality of life, and what it showed is that despite the toxicity and cost of mitoxantrone, the patients who received mitoxantrone front line had a better quality of life.

They did a series of other assessments that related to cost economics and identified that it was cheaper for the Canadian community, that there were patients going back to paying taxes sooner, they were spending less time dying in hospital, so this was a drug that actually did

influence outcome.

Dowling and colleagues in the Annals of Oncology, looked in a little more detail at the whole issue of studying that trial, so this was a retrospective analysis, and what it showed very clearly was that while mitoxantrone had been quite useful, palliative response did not predict for survival, and there were major discontinuities between quality of life measures, PSA response, and ultimate survival.

So, that should make us very, very cautious about interpreting or overinterpreting data. I always think it is a good thing to suck up to the Chair, so I did want to show this slide that I stole without apology from Dr. Maha Hussain at a previous time. Maha, thank you for providing the slide. I have jazzed it up a little bit.

The point of this slide is to demonstrate simply that the issue of variability of quality of life is not an inherent characteristic of the agent mitoxantrone. These are a series of drugs that hold up a cell cycle in a fashion analogous to

Taxol or Taxotere, and what it simply shows, as you look down at the columns on the right, is that there is a variability of survival, there is a variability of pain improvement, and there is a variability of PSA response.

So, it simply says the Venn diagrams of assessment of outcome do not overlap very well irrespective of which agent is being used.

Dr. Eisenberger, at our symposium, presented data from TAX-327, one of the two pivotal trials that seems to have been responsible for the approval of Taxotere for prostate cancer, and this is important work.

I am showing this just to show that both studies give us the same message. If we look at the different indicators of outcome, again looking at the denominator of cases for which data are available, you can see that there is a really quite dramatic heterogeneity of interpretation, and depending on what you want to draw from this set of data, you can draw pretty much whatever you wish.

I think there is a general consensus that

in each of the parameters, docetaxel won and that the difference wasn't all that great.

This may be a good time to quote Benjamin Disraeli, one of the former prime ministers of the United Kingdom, who was quoted to say, "There are lies, damn lies, and statistics," and that may well relate to the way the confounding difficulties we have in interpreting data from the prostate cancer environment.

I think this is an important study to show because it shows how the community can make serious mistakes. Now, this was an important study published by Tom Beer and his colleagues from the University of Oregon, and they looked at the combination of Taxotere and a vitamin D analogue, and this hit the headlines in virtually every major publication in the USA.

I was puzzled because this was a Phase I study, and it was a Phase I study in which there were indices that I have summarized there. They identified the ability to achieve PSA response, survival was not an endpoint, because the numbers

which are small, and it was a Phase I study, and what was puzzling was that there was a complete discontinuity between the different indicators of patient-driven outcome, and yet the press heralded this as a major breakthrough.

So, I think what it shows us is that we have to be very careful in interpreting quality of life data.

Finally, Tannock and his team have also addressed in specific ways the impact of placebos in oncology, and I think it is always good to remind ourselves something that we know, but that we sometimes forget in dealing with prostate cancer, which is that the placebo effect can certainly have an impact on quality on life.

It generally doesn't improve performance status and it generally doesn't improve survival, but it does alter quality of life, so that means that we need to be looking at the quality of life assessments very carefully and assessing them in the context of the interpretation of the placebo effect.

So, my take on patient reporting of symptoms is that if we incorporate them into the evaluation of new agents, it will lead to an additional stage response migration. These will one day be very useful tools in the assessment of prostate cancer, but I think that the tools that are extant at the moment are not ready for prime time. We certainly need to be incorporating them into our assessments, but they shouldn't be the drivers of decisionmaking.

PSA response versus symptom response versus toxicity lead to a disconnect, and that may sometimes be because big trials don't allow for a detailed structured assessment of what are the factors causing that disconnect.

So, it leads me to feel that this area should be regarded as work in progress by the FDA in its formal and structured evaluations of new products. Survival has been the standard. It is my personal belief, supported by some data that are not yet incontrovertible that time dependent PSA kinetics will ultimately be a very useful surrogate

of outcome, but we will need to apply Howie Scher's states model such that we acquire data for time dependent PSA kinetics in a series of different clinical contexts.

One size fits all simply won't work in giving us a meaningful evaluation of new products that come into the marketplace, and most particularly those that are cytostatic in their type.

We will still need to do well-powered, large, carefully designed, structured randomized trials, and those trials should require surrogates to be evaluated including quality of life and patient reporting, PSA response, PSA time dependent kinetics, perhaps markers of bone turnover, and we shouldn't throw out survival just because it may be a confounded variable.

Ultimately, we haven't figured out an optimal way of assessing the cytostatic drugs. We spent a lot of time at the symposium discussing those, and I am figuring Howard will probably talk a little about that. I feel personally that this

is work in progress, so I have stayed away from putting up the assessment of cytostatic drugs in a structured fashion, because I think we are still learning how to do that.

Ultimately, I think we are not ready for definition of a new era, but I think the FDA is very well positioned to demand certain things of the companies and the agencies that produce new medications to allow us to finally define what is the new era in prostate cancer treatment.

Thank you.

DR. HUSSAIN: Thank you, Dr. Raghavan.

Our next speaker is Dr. Alison Martin from the NCI. She will be addressing the NCI's Portfolio of Prostate Cancer Treatment Trials.

NCI Prostate Cancer Treatment Trial Portfolio

DR. MARTIN: Good afternoon, Madam Chairman, members of the panel, Dr. Pazdur. Thank you for the invitation to present.

I was considering how to be useful to these proceedings since many of the investigators that my program, the Cancer Therapy Evaluation

program, funds through the cooperative groups are here, have reported their trials in prostate cancer, including with surrogate endpoints and including today.

So, I decided to step back and focus on our program as a capacity to further address the questions that come up in these proceedings and at other times. I have talked myself into the possibility that our program is at a crossroads in the sense that we have approved more concepts this year for prostate cancer treatment than any other year in the past decade, and that we have seen more hypothesis generating for surrogates than at any other time.

So, I would like to encourage us all to think about how we can maximize the capacity across all of these trials.

Currently, I think we are standing from a position of strength and weaknesses. With regard to some of the strengths, there are a number of randomized treatment trials that are mature, which provide us with well-defined cohorts, high quality

and long term follow-up and defined treatments.

We heard about some of them a year ago at the PSA Workshop RTOG 92-02, which Dr. Sandler has reported on, and we will hear again from Dr. D'Amico, which looks at PSA doubling time as a surrogate for survival in high-risk, early stage patients.

You have already heard and will hear again later this afternoon about the two trials, SWOG's 9916 and Aventis-sponsored TAX trial that led to the approval for docetaxel, and by finally identifying a treatment which had an impact on survival in the randomized setting, it provided an opportunity to look at surrogates across arms and across trials.

Separate from the randomized trials, there are significant longitudinal databases from certain cancer centers with large cohorts and CaPSURE/CPDR.

There are limitations also. You have heard from Dr. Raghavan quite eloquently about the population issues and the heterogeneity, coupled with stage and assay migration. There are also

design issues, which is that most of the randomized trials weren't prospectively designed to ask a surrogate question or consider the power associated with that.

Furthermore, the schedules for the collection of PSA or other intermediate markers, such as bone, may not have been sufficiently specific. Even if it were within one trial, it may have differed across the trials.

There have been treatment issues limiting us in our questions and answers. One, the fact that some treatments, for instance, hormones can interact with the surrogate of interest, or that there has been a lack of effective treatments to allow validation of the surrogate's association with survival.

Now, I would like to move from separate from limitations of individual databases. Once we have identified a database that may be contributory, there are difficulties we have experienced in terms of analyzing those databases in a timely fashion using the same surrogates of

interest.

It is rare that people turn over their databases to someone else of whom it is a priority, so it requires a collaboration which is sometimes difficult to arrange and perhaps best thought of prospectively.

Other trial design issues, whether we are looking at data mining existing databases or looking forward to how we should consider the designs that are coming up this next year, or whether we want to ask questions about PSA as a prognostic factor, as an eligibility criterion to make our cohort more homogeneous, or to choose a high-risk cohort to allow us to arrive at an answer sooner.

Do we want to use PSA as an outcome measure, and, if so, which outcome? Do we want to use it as an indicator itself of cure, for instance, in an initially diagnosed patient treated with a radical prostatectomy who either did not nadir or has a return of the PSA to a certain level, is that sufficient to tell us that the

physician prescribed treatment, which was intended to be curative, had failed, or do we want to ask whether even though they were not cured, we need to know how this correlates to survival, does that depend on the adjuvant or neoadjuvant treatment given, and the risk classification.

Are we interested in PSA as it correlates to some other measure of clinical relevance, such as those listed on the slide, and then which PSA parameter are we to use? Once we choose, what is the magnitude of change that we think will be relevant and the strength of association with the outcome of real interest.

Potential opportunities in the near future. We have approved 6 and there perhaps will be a 7th later this year, treatment concepts, and we expect actually they may open in the same year that they are approved due to a number of new processes, one, the collaboration with the FDA at the time of concept approval, and also our collaboration with investigators and the generation of the protocol. Rather than holding our review to

the end of the process, we are integrated into the process.

Of these approved concepts, they will be accruing in each of the clinical states that the previous speakers have mentioned. I have taken the liberty of borrowing the clinical state slide from both Drs. Raghavan and Scher, and inserted the pending trial next to it for ease of reference.

The goals are as previously listed with some of the goals added for the cohorts that have clinical metastases, either non-castrate or castrate.

Although I didn't list survival of prostate cancer, specific mortality is a goal in the first two boxes, and they weren't previously either, it should be stated that, of course, survival is important when any intervention is given. It is just that there are also comorbidities and competing causes of death and nearer term outcomes that may be relevant also.

In localized disease, there will be a trial with hormone therapy coupled with

docetaxel-based regimen in two cooperative groups. In hormone-resistant rising PSA state, there will be a vaccine trial, and as currently planned, while survival will be collected as a secondary endpoint, the primary endpoint is the incidence of clinical metastasis.

The other trials are androgen deprivation therapy with a backbone of docetaxel, and lastly, in the population that showed the docetaxel had a survival benefit, the addition of either bevacizumab or Atrasentan.

In conclusion, these are some of the strategies we have thought of and we would welcome other comments and suggestions on how to maximize the return from these trials.

Number one, of course, nesting a surrogate question into the therapeutic trials. There are probably still databases, well, I know there are databases that could be mined for hypothesis generation of surrogate endpoints, but at any rate, can we prioritize the most important, if it's PSA response by 50 percent at 3 months, so be it.

Are there others, how many can we incorporate prospectively without suffering from multiple comparisons, one, two, three?

Can we, while we are looking at surrogacy, compare it to survival, but, as well, some other intermediate endpoints of interest?

Separate from embedding a surrogate, can we systematically create a comprehensive database for subsequent interrogation, so that if our PSA definitions change or we are interested in some other question, we can interrogate the database across trials, not just within trials?

To the extent possible, can we harmonize the amount of PSA data collected prior to treatment to look at new risk classifiers? Can we standardize when they are collected, when bone scans are collected, so that we know when there is time to clinical metastases in a more rigorous way?

Do we want to know when a patient becomes castrated, if they have been treated with hormones?

There will no doubt be, in the future, more informative markers, although we may not know

exactly which ones they are now, and to the extent possible, we would like to encourage specimen banking depending on the stage of disease, blood or tumor.

Lastly, two other partners that would be helpful to our efforts right now are to prospectively identify what industry trials are relevant to the clinical states, and try to harmonize our schedule of collection of data.

We are opening six or seven trials this year. That certainly does not represent very many in each clinical state, and we would like to work with our industry partners and the FDA to encourage industry.

Lastly, the Cancer Diagnosis Program has an initiative PACCT, the Program for Assessment of Clinical Cancer Tests. They have worked with breast cancer field and color cancer to identify new risk classifiers, and they have made a commitment this year to convene a strategy working group to further identify trial designs and questions with PSAs and other markers.

With that, I will conclude. Thank you.

DR. HUSSAIN: Thank you, Dr. Alison.

Our next speaker is Dr. Howard Scher from Memorial Sloan-Kettering. He will discuss similar endpoints dealing with accelerated approval for clinical trials in castration resistant/hormone refractory prostate cancer.

Toward an Endpoint for Accelerated Approval for Clinical Trials in Castration Resistant/ Hormone Refractory Prostate Cancer

DR. SCHER: Thank you very much.

I won't try to mimic Derek's accent, but I will echo some of the same themes.

What I think is becoming apparent from the previous presentations is that we are, in fact, in a position to ask the questions which will allow us to better understand different intermediate endpoints, because for the first time, we are actually conducting trials that are large enough and enroll a sufficient number of patients to address meaningful questions.

So, just briefly to summarize where we

have been in terms of outcomes assessment, we all recognize that the manifestations of prostate cancer are very, very difficult to assess. The clinical realities are that PSA levels guide what we do in clinical practice.

We are now faced with the challenges, PSA response outcome or progression measure which is reasonably likely to predict clinical benefit and form the basis of an accelerated approval.

I would like to argue that these trials can be designed, but before we can actually say anything about the rule of PSA in outcome assessment, we actually need to prospectively design the trial, as you have heard from previous speakers, in which the endpoint, based on the marker, is embedded.

So, I would like to think a little bit more in terms of the disconnect that has been discussed earlier in terms of PSA response, symptom assessment, and effects on survival.

All of these can be important clinical endpoints, and if we start thinking about treatment

objectives across clinical states, we can really divide them into two categories, which I will call eliminate/relieve versus prevent or inhibit progression.

If we start thinking about the patients who have progressed post-hormonal therapy, so-called castration resistant or hormonal refractory state, we are really now dealing with two discrete populations, and they represent patients who have received hormonal therapy without any evidence of clinical metastasis on physical examination or on an imaging study, the so-called rising PSA castrate state, and those patients who first received hormonal therapy at the time of objective detectable disease on an imaging study or physical signs or symptoms of disease, which we have called the clinical metastasis castrate group.

I will be focusing most of the discussions on those patients who have overt metastasis at the time hormonal therapy was initiated, although certainly the discussions will hold for patients with a rising PSA.

What we are dealing with again is the battle or race between death from other causes, which is inevitable, versus death from disease, which is what we are trying to prevent.

So, if we think about patients really in two categories, if there are manifestations present, we will use those manifestations to assess a response measure designed to either eliminate a symptom, relieve or control it.

If it is not present, we can think in terms of how do we prevent it from occurring in the future, and here the risk assessment models are very important in terms of how do we know that the patient is likely to need therapy for a specific event, and we have a very unique opportunity to data mine some existing databases with regards to eligibility for trials.

If we think about what the outcomes are as you are sitting with the patient or explaining a trial to your colleagues, you would like to be able to say that what you have assessed is clinically relevant and of tangible and concrete benefit, and

obviously, we will factor in the risk/reward ratio before we think about therapy.

Looking back at the approved drugs, you can see how this eliminate/relieve or prevent objectives has been played out. The bisphosphonates, radiopharmaceuticals, chemotherapy, the original approval of mitoxantrone and prednisone were based on response measures that showed the elimination or relief of symptoms.

We can think of delaying symptoms or change in therapy, skeletal-related events in terms of a progression endpoint, and even death from disease is a progression endpoint because you are preventing death from cancer, but none of these approvals were based on measure of tumor progression, and none of them were based on a post-therapy change in PSA.

So, we think back now in terms of eliminate/relieve. We are thinking about the manifestations of disease that are present, how we relieve those manifestations, a response algorithm, and figure out what they mean.

It was interesting looking across our own series of patients at MSKCC treated with chemotherapy versus the two recently reported SWOG-9916 and TAX-327 in terms of the frequency of the different manifestations of prostate cancer.

As you can see, the frequency of measurable disease is on the order of 20 percent. There is a component of patients with visceral metastases. Arguably, these have a worst prognosis. Many of the so-called nodal sites we are looking at are actually very small, and one can argue what their clinical significance is, particularly when you are looking at the changes in size.

The dominating theme in this patient population is osseous metastasis and a rising PSA, and symptoms are variably reported, and Dr. Raghavan gave a very elegant discussion of the issues surrounding quality of life, but about 35 to 40 percent of patients will have some symptoms which are recorded as significant, but again the dominating symptom complex that we are treating,

trying to relieve or prevent from recurring relate to complications of bone disease.

What are the outcome measures? If you are looking at disease in the primary site, there are no defined criteria. For soft tissue disease, we have been mandated to use RECIST, which has problems because it relates only to your relatively unique proportion of the symptoms of prostate cancer. It does not address issues related to bone metastasis or PSA.

For bone metastasis, there is no standard criteria for response, and I will go through some of the post-therapy PSA change metrics. In terms of assessing quality of life, we always feel better if there is pain relief, but we also like to see what are corroborating domains, that is, the patient was more mobile, more active, slept better, less constipated because of analgesic uses, and we have all pretty much agreed in the community, if you will, that the group categorizations of CR, PR, and stable disease are really of little value when it relates to clinical trials.

So, thinking about the post-therapy PSA endpoints, one can look at decline, no rise or fall, undetectable, normalization. Some of these are relatively infrequent occurrences unfortunately with our available therapies, so most of our reports have focused on either a decline by a fixed degree, most reporting 50 percent, or more recently, no rise or no fall at a fixed time point, but whatever decision rule one is looking at in the Phase II setting will vary depending on what type of drug you are studying.

The differentiating agent, for example, may make the PSA go up before it goes down. The cytotoxic drug may arguably make the PSA go down. Otherwise, it is likely to be ineffective, but whatever response measure is used in most criteria, the change that you see is required to be detected over a period of time.

There was a consensus meeting in the late 1990s. A consensus was described for a PSA response, which required a 50 percent decline from baseline, and as you have seen here, in this

particular illustration, the decline was confirmed on multiple occasions.

The reporting standard has become 50 percent or greater decline as a "PSA partial response," which is confirmed by a second value four weeks or more apart, but even within these criteria, there was recognition that there are other issues of relevance, as stated, different endpoints can also be reported.

Time to PSA progression and index of the durability of the response was of interest, and in order to be considered in a response category, there could be no evidence of clinical or radiographic progression, again arguing that other manifestations of disease must still be monitored.

Looking for associations of PSA decline and survival, again, a 50 percent decline versus no 50 percent decline. These particular analyses were done using a landmark method, that is, the patients had to live a period of time before survival distributions were analyzed, and these results were analyzed on an independent data set, but in both

situations, where there was a 50 percent decline or no 50 percent decline, no rise versus rise, again at 12 weeks, there did appear to be a survival benefit for the patients who achieved this endpoint, and, as illustrated, several groups have shown this.

More recently, other measures are being considered, a variety of metrics. In this case, as I am sure Dr. D'Amico will discuss further, the ratio of the post- versus pre-therapy PSA slope, but with the consistent theme that one sees that regardless of the metric used, these trials are reporting a difference in survival based on the outcome measure.

So, clearly, we are at the point now where the associations between a PSA decline have been demonstrated. This makes sense. If you are studying a cytotoxic drug, you kill cells, PSA should go down.

This may not apply, as Dr. Raghavan mentioned earlier, to non-cytotoxic agents or, for example, a drug directed at a component of the

metastatic process, for example, an angiogenesis inhibitor or a specific bone targeting agent that may not necessarily kill cells.

But missing in all these analyses were positive randomized trials to explore the surrogacy questions.

I won't detail these trials, these have been reported before, and we are all familiar with them. Suffice as to say that in 2004, there were two trials reported which did show a survival benefit, which allowed the exploration of whether a specific PSA outcome measure was associated with survival.

Again using various criteria for surrogacy, in this case the Prentice criteria, Dr. Petrylak and his colleagues asked the question whether achieving any PSA value--it could be a single value--below 50 percent of baseline was associated with survival, this performed in the context of the SWOG-9916 trial.

Again, as shown earlier by Dr. Raghavan, there was a first qualification required that there

be a survival benefit for therapy. Looking again at the association between the 50 percent decline and no 50 percent decline, a significant difference of 50 percent improvement if one is looking at the survival distributions.

When one accounts for the 50 percent decline, the treatment effect disappears. So, this would appear to satisfy the Prentice criteria, but what has been misinterpreted is whether or not these results can, in fact, be extrapolated to other trials, and the answer is no, this would apply only to this trial, and it may not necessarily be applicable to other therapies.

But it did suggest at least for this specific treatment that a 50 percent decline from baseline could be used as a surrogate for survival, but again, we do not have multiple trials in which to address this particular question, and at this point it could only be listed as a hypothesis.

So, TAX-327 was like was reported, showing a similar PSA response rate as we discussed, and in this particular trial, although the PSA response

rate as reported was identical, there was only a survival benefit demonstrated for the Q3 week arm. For patients who received weekly therapy, there was no difference in overall survival. So, this raises the question as how much survival is explained by a post-therapy PSA change. In order to be a true surrogate, you like all of the survival to be explained by the post-therapy PSA change.

This led us to look at what is the association between time dependent changes in PSA and relative risk of death. This was again a retrospective analysis of patients treated in Phase II trials.

You see the risk of death for a very low PSA appears to be higher than patients with a moderate level PSA, as illustrated by the dip in the curve, and as the PSA levels go up, associated with much higher tumor burdens, the risk of death increases, but the amount of survival that was explained in this analysis was only about 17 percent, and as my statistical colleague, Dr. Halabi reminds me repeatedly this is not enough to

base treatment decisions.

So, looking back at some of the other trials that have been reported, it was of interest in Dr. Crawford's presentation, looking at the construct of a 50 percent decline in the context of SWOG-9916, association with survival was about 22 percent.

Using a metric of change in PSA velocity, 16 percent, Dr. D'Amico's slope changed 22 percent, similar to ours, so again there is a significant amount of survival which does not appear to be explained on the basis of PSA decline.

What about palliative response? Again, to show how Dr. Raghavan and I are thinking in a similar fashion, which is scary to some degree, there has clearly been a disconnect between the observation of a palliative response and a PSA response.

This was the work of Dr. Tannock cited earlier, of looking at mitoxantrone/prednisone trial, which did lead to the approval of mitoxantrone and prednisone, and to my view

established a very important principle that systemic chemotherapy could provide palliation of symptoms of the disease.

Looking at the PSA response rates, the palliative response rates appear to be similar, but in the proportion of patients who achieved, looking at PSA response relative to palliative response, only 60 percent of patients who achieved a palliative response had a decline in PSA.

This was very dramatic in terms of the prednisone arm where only one patient showed a significant decline in PSA, although a proportion did show a palliative response.

So, where does this leave us in terms of PSA change and survival? Trial 9916 showed that there was an association of PSA decline and the treatment effect was eliminated when adjusting for the intermediate, did not see the same effect in both arms of the TAX-327 study. The Q3 week arm was the only arm to show a survival difference.

Although we have used different metrics in the construct, and looking at retrospective Phase

II data, and post-trial analyses of randomized comparisons, the amount of survival that is explained appears to be very similar, about 20 percent.

Does this make sense? Yes, it does make sense, because if you think about what does PSA do in terms of prostate cancer progression, it is really not known. There has been some speculation as to its modulation of growth factor effects, but one could understand that PSA alone does not necessarily drive a prostate cancer cell.

We still have to remember in terms of clinical benefit that there is this association of a PSA response and a palliative response, which reminds us that we must continue to monitor the other manifestations of the disease, and we all know based on pathologic studies that not all cells within a tumor in fact express PSA, so we may be dealing with a component of clonal selections.

But a limitation of all of these analyses is that they were retrospective and they were not the results of prospectively designed trials

looking at a question around the marker.

So, maybe if we have so much difficulty with response, maybe we should think about the failure to progress or looking at a non-progression endpoint.

If one considers the importance of following patients using different measures, both physical assessments, symptom assessment, PSA, and imaging studies, perhaps we can start getting a better index of whether or not we are changing the disease particularly if we are enriching the population that we are treating for high risk of a clinical event.

If you are thinking exclusively about overall progression of disease, you don't really have to worry about surrogate, you have defined it on a clinical endpoint, and it is really going to be a measure that will be drug mechanism independent depending on the question that you are asking.

So, if we think about preventing progression of disease, we do have criteria for

some of the manifestations. For measurable disease, we do have RECIST. We do have a problem in that we do not have scan criteria which have been standardized to assess serial changes in bone scan.

We do know that in about 70 to 80 percent of cases, however, that PSA elevations do precede other measures of progression, so this may be sufficient and certainly a point of discussion of whether this type of endpoint could be considered in the context of a prospective study.

For quality of life measures, again, there are validated instruments. These are not 100 percent concordant with PSA, and death from disease is clearly an endpoint that will not be debated.

There has likewise been as a result of collaborations in the academic community, standardization of reporting and definitions of progressions that we accept.

This is an illustration from the JCO publication in 1999 showing a definition of progression by PSA, which includes a 25 percent rise from the nadir as the time point, but again

keep in mind, as shown earlier, that we can see benefits which are clinically significant or at least lead to drug approval without an effective PSA, which is clearly illustrated by the endpoint used for the approval of zoledronic acid, which was a reduction in skeletal-related events at 15 months in a patient population at risk.

So, we have been asked to put up a bar, and I have been debating with many people what this bar actually means, because what we have been challenged to do is to come up with a measure that is reasonably likely to predict clinical benefit.

The regulations for accelerated approval are very clear. They require substantial evidence from well-controlled trials regarding a surrogate endpoint. The problem that we have had in prostate cancer clinical trials, too few studies, too little participation by both patients, physicians, and overall community at large in these studies.

Until recently, the trials were underpowered and undersized. As shown by Dr. Raghavan earlier, the response observed with

estramustine and vinblastine in the early 1990s was not dissimilar to what we are seeing now, yet the Phase III trials that were designed were not of sufficient size to actually address the survival question.

Although we have looked at various associations between PSA outcome measures and survival, these are all retrospective analyses. They were not derived from trials prospectively designed to test the value of the surrogate measure.

So, as we look forward, we do have several challenges. We have to balance the clinical realities of practice, that treatment is rarely continued if the PSA is going up, and this is one of the problems I have in terms of slope modulation.

The patients comes in with a graph, it is going up, they are not happy. If the treatment is going down, it is very hard to stop treatment. That is reasonable, although in many cases, there may be other measures suggesting that the treatment

is no longer working.

We have seen in clinical trials that there are specific protocol-mandated definitions of progression. That can lead to premature discontinuation of a drug. This will relate primarily to some of the definitions that have been applied to the use of bone scanning agents.

One or two new lesions dictates progression, and I will illustrate a couple of situations where that, in fact, may not be the case. What we really need is clear evidence of progression before treatment is continued.

It is not as if we are withholding tremendous options, so an approach, when I am discussing treatment with a patient is trying to really make sure it is either working or not working before you abandon it, because you don't necessarily know what will be next, and you don't want to abandon a treatment that may, in fact, be helping an individual.

So, here is an example of a patient. Actually, this data was generated yesterday, so

it's contemporary. Here is a patient who is progressing after previous microtubular targeting therapy.

His PSA went up to the low 300s. The date, which you may not be able to see, is early October of 2004. His PSA after this next chemotherapy has been going down. He is asymptomatic, his pain is resolved. His bone scans are stable.

He would not meet the criteria for a PSA response, and arguably, this is a patient who is benefiting, and even though he has shown a degree of myelosuppression, he religiously comes in for his treatment. So, this patient would be missed as a responder or a patient who is benefiting from therapy if we were stuck with a 50 percent decline.

Here is another illustration. If you look at the patient's baseline bone scan on the upper left, there are some lesions visible in the skeleton and in the manubrium.

At the three-month scan, there were two lesions that appeared, one in the rib and one in

the vertebra. By some protocol criteria, this would be considered progression. The patient was asymptomatic. His PSA kinetic curve is on the right. You can see the PSA is going down.

Treatment was continued. A bone scan was done a six months. It remained stable. Patient remained asymptomatic and subsequently, there was an improvement in these lesions.

So, this mandates very cautious interpretation of bone scans, something we have to consider as we are designing trials going forward.

So, what might a prospective trial look like which is powered on survival, which has an intermediate endpoint embedded, which might be considered for interim approval?

The first question one might ask, and this is an example of powering a trial on survival, does Treatment A prolong life relative to Treatment B? In the first line setting, this could be patients with no prior chemotherapy, obviously, this would be going against a standard of Taxotere, or in the second line setting with one prior therapy, one

could power on trial on survival, for example, a 25 percent improvement, and secondary endpoints might include a PSA response definition using the consensus criteria, for example, a 50 percent decline, a PSA progression criteria. Again, there are consensus criteria for same, or a composite endpoint that includes PSA.

It is obviously in yellow, which is where my bias happens to be. One could certainly consider an accelerated approval based on an interim evaluation assuming the trial endpoint was met, with the proviso that the trial accrual and monitoring continue until accrual was complete, the analysis complete, to assess the primary endpoint, which in this case would be survival.

As mentioned earlier, it becomes critical in these trials not to stop following patients at the first sign of progression. They need to be followed and monitored at fixed intervals after treatment in order to better define the clinical course if we are going to validate some of these endpoints.

The CLGB has designed one such study, and Dr. Halabi was kind enough to allow me to present this. The PI will be Dr. Kelly at our institution. They are studying whether the addition of an anti-androgenesis agent Avastin will improve the outcomes to standard first line chemotherapy.

The primary endpoint is looking for prolongation of life. The secondary endpoint will look at a progression-free survival endpoint comparatively between the two regimens. Eligibility is risk based, based on nomograms and risk of mortality with stratifications based on a nomogram that was developed by Dr. Halabi, and all symptoms of disease and manifestations will be recorded.

The primary endpoint is to look for a reduction in the hazard ratio of death of 25 percent using a two-sided analysis, and they will explore associations between progression-free survival. This is not intended as an approval study.

Another example might be in the second

line setting for a cytotoxic drug - does this new cytotoxic drug (a) prolong life relative to mitoxantrone and prednisone, for example, we can discuss what the comparator might be, in patients who have received one prior chemotherapy.

The secondary endpoint might be to compare the PSA or overall progression-free survival of the two regimens. Again, the trial would be powered on survival, and consider PSA progression or a composite that includes PSA for a potential for accelerated improvement as enrollment on the trial continues to reach the primary endpoint.

So, where we are now? Clearly, we still recognize that this is not a straightforward disease to manage. There are clear difficulties in assessing response and outcomes. We must address within our trials the clinical realities that PSA levels and changes in those levels do drive treatment, and the question remains for us to prove prospectively whether there is a PSA response or progression construct that can predict for true clinical benefit and form the basis for an

accelerated approval.

But I clearly believe we are in a position to do those trials, and there has been a demonstrated commitment to complete the trials of adequate size and power, so that we can actually address these questions going forward.

Thank you very much.

DR. HUSSAIN: Thank you, Dr. Scher.

Our final speaker is Dr. Anthony D'Amico from the Harvard Medical School, who will discuss the design of clinical trials for select patients with a rising PSA following primary therapy.

Design of Clinical Trials for Select Patients With a Rising PSA Following Primary Therapy

DR. D'AMICO: While we get the screen up, I want to thank Dr. Pazdur for letting me part of this experience. Actually, it has been a wonderful thing to put this set of data together, and it has been a lot of fun.

I also want to thank Johanna Clifford and Diane Spielman for all the logistical support that you helped me with during the course of getting

here.

I never used to put humor into my talks until I met Dr. Raghavan. There was a talk that he was giving once at the course we have in Boston every other year, and I was very impressed with his delivery, in addition to the information that he gave.

He said to me, though, today on the way in that you are not supposed to have a joke prepared, you are supposed to do it on the fly. I was thinking to myself, well, maybe when I reach his age, I will be able to do that, or maybe if I reach his age, I will be able to do that.

What I would like to talk about here is a very specific disease state, the rising PSA after surgery and radiation in a very well-defined population, people who have, in some people's data sets, achieved "surrogate for cancer death," with a very specific endpoint that involves the standard endpoints - death due to prostate cancer and metastatic disease predates that, and then also consider some questions that we could raise about a

PSA construct.

Now, I am a believer that it is more important that the information that you give is concise and important more than it being excess volume, so contrary to Dr. Raghavan's suggestion, I am going to tell you a little thing I had planned, because it sets the stage for this talk.

I enjoy martial arts, it is something I have been doing since I am a child, and this is a story that I heard once that I really found very interesting.

There is a young gentleman who wants to enter a Buddhist monastery, and he is told at the age of 12, "Well, listen, you know, this is a strict place, there is vows you have to take, something called chastity, poverty, silence." He says, "In fact you only get to speak two words every five years." He says, "I want to do it." So he goes into the monastery and does his first five years, and when he comes out, okay, "You have got two words, you're 17 now, what are they, and he says, "Bed hard."

Okay, fine. Go back on in. Comes out at the age of 22 after 10 years, he gets two more words, and he says, "Food cold." They look at him, sort of a seniors look back and forth and shake their head. "We will give him one more try." After the 15-year stint at the age of 27, he comes out, and he says, "I quit." They said, "Fine, you have done nothing but complain since you got here."

So, in terms of this particular construct, I am going to start designing a clinical trial from the first slide, and the first thing we need to design in a clinical trial setting is patient selection. Let me focus you again on the disease state that we will be talking about, is the rising PSA following surgery or following radiation.

In my mind, and there may be some dispute about this, if one really wants to have a "alternative" endpoint to the standard endpoints, the place where it is needed most in my mind is the earlier states of bad disease to come, and not the endpoint of the disease where they have only got an average 18 months to live.

I think that, you know, the TAX-327 and the SWOG-9916 study from accrual to publication was four years, which isn't bad. I mean that survival-based studies in hormone refractory metastatic disease are not unreasonable, but in locally advanced prostate cancer, the bolus study, the ORTC, the RTOG studies, 92-02, a study we ran in localized high-risk prostate cancer, radiation plus or minus hormones from start of accrual to publication was 10 years.

This is where, if anything, we need help in defining endpoints that are clinically meaningful and earlier. So, with that said, we have a huge amount of information, and as I go through each of the centers or cooperative groups that have contributed, I will recognize them.

There has really been a national effort that has been designed at exploring PSA doubling time following radiation or following surgery, and I will take you through all the information that has been published to date or soon to be presented, and I have gotten permission from the investigators

in ASCO where some of this will be presented to show some summary slides.

But what we have learned is that the doubling time following radiation or surgery is significantly associated with time to cancer-specific death following the institution of PSA failure on which the doubling time calculation is based.

This data comes from a series of multi-institutional and single institutional studies, and I am going to highlight four of them because each one has a unique characteristic.

The first one is RTOG 92-02 where patients managed with radiation were randomized to short- or long-term hormones. The next one is a multi-institutional database, 44 institutions around the country, CaPSURE, which is run through Peter Kal [ph] on the West Coast, and CPDR, which is run through Jud Mool [ph] and Dave McCloud here at Walter Reed, and then two single institution studies of importance, Johns Hopkins and Barnes Jewish, Johns Hopkins because this was a place

where no one got hormonal therapy for a rising PSA until the bone scan was positive.

That is a unique data set, which tells us something about the natural history of a rising PSA patient following failure after surgery; and then the Barnes Jewish, Bill Catalona's database, which I will show you some results from, and will be published later in the year, from a group of men who were prospectively screened.

Everybody had serial PSAs, so this is the stage migration issue that Derek Raghavan was talking about. We will look to see what doubling time does in that particular group, and how significant or lack of significance is it, so let's go through it.

This is from Dr. Valacenti and Dr. Howard Sandler. This is the schema for RTOG 92-02, and this study has been published in the Journal of Clinical Oncology, but what is soon to come is the slide that follows.

The two arms are shown, locally advanced prostate cancer T2c-T4, Pretreatment PSA is under

150, 1,500 patients or so randomized to radiation with 4 months of hormonal therapy or 2 years and 4 months.

This is what they found. They applied the full Prentice criteria to the model. I am not going to present that and I will get to why later. But the one point I am going to bring out is that when they looked at PSA doubling time, and specifically this is for a break point at 1 year, they found a 6-fold increase in cancer-specific death. The confidence interval is pretty tight, 4 to 9, as shown.

For this particular parameter, for the first time really in a group of men managed with radiation and hormonal therapy, it hasn't been done before. It has been done for radiation, it has been done for surgery. These are guys getting radiation and short- or long-term hormonal therapy, so this is new information.

There is the cancer-specific survival plot or 1 minus the cumulative incidence of cancer death, stratified by the doubling time, a

significant difference.

Of note, I will just point out that if you look at the guys with the doubling times less than 12 months, which is the dotted curve at the bottom, by the time you get out about 5 years, already about 25 percent of these people have died of prostate cancer, and it is a doubling time less than 12 months. That story is going to evolve.

Here is the study that was written up by CaPSURE and CPDR databases, that multi-institutional database several years ago now in JNCI, and what was shown here is that in a select group of people with a doubling time less than 3 months, which are the green and black curves at the bottom for radiation and surgically managed patients respectively, that the median survival was only 6 years.

This stood in contradistinction to the Pound's paper from Hopkins, which said the median survival for guys with a rising PSA is 13 years, until you put the things together and realize that the Pound data incorporated everybody on the plot,

and we get to the very important point that this makes, which is in the rising PSA cohort, all patients are different, it's not one group.

In that one state of disease, you have got a multitude of biology, from the very worst to the very best, and the very worst can be characterized by the short doubling times, the very best by the longer ones, and there is the basis for patient selection for a clinical trial.

Let's go to the rest of the data. The hazard ratio from that data set was 20, a 20-fold increased risk of cancer-specific death if your doubling time was less than three months as opposed to three months or more in contrast to the value of 6 when the doubling time break point was 12.

Now, here is an interesting slide that hasn't been shown yet. This is Dr. Catalona's screened database, all these men, 8,000 or so of them have had a screened PSA each year. Their median PSA of diagnosis is 4.2, so they are very early, but the fascinating thing to me is that that red and blue curve at the top, red is overall

death, Kaplan-Meier incidence of death, and blue is cumulative incidence.

If your doubling time is less than 3 months, even though you were screened, you still got a very high death rate, and the point I want to make is if you look out five years, where the numbers at risk are still reasonable, overall death and cancer death are the same.

That goes right along with this doubling time less than 3 months being very highly correlated, if you will, a surrogate for cancer death, even in a screened population.

In the population of them at longer doubling times, cancer death and overall death are about 50 percent of one another. You can see if you work it out, half of death is due to other causes, half of death is due to cancer in the orange and the green curves below.

But the striking thing that I find here, as you look at the numbers at risk at time zero, the percent of patients who have a doubling time less than 3 months in a screened cohort is 7

percent, and in the CaPSURE or CPDR, what happens in the community where some people get screened and some people don't, it is 20 percent.

So, it is very interesting to me that the proportion of men with bad biology at the time of recurrence in the screened group is much less as you would probably expect than it is in a relatively normal community population.

It gives us some estimate, here is 0.2, at the size of the population we could enroll into a study where the patient selection is based on doubling time, and I will tell you what the study is in a moment. Those are treated patients with surgery.

Now, this is the slide from Dr. Parton, Dr. Eisenberger, and Dr. Friedland at Johns Hopkins, and this, too, is to come, but it is a fascinating description in my mind where they have broken out surgically managed patients, doubling time now not as a categorical, but as a continuous variable, and the adjusted hazard ratio of 0.86 with tight confidence intervals basically says that

as your doubling time goes up, your risk of cancer death goes down by about 14 percent per unit increase in doubling time.

But look at the plot here of cancer-specific survival, the largest doubling time is at the top, the less than 3 months at the bottom. Again, you are getting that 5- or 6-year median survival in that doubling time less than 3-month group. The same number we are seeing it over and over again, multiple databases showing that that doubling time less than 3 month group has got about 5 or 6 years to go.

But it is nice to see that there is a stratification in survival that goes from the worst doubling times to the best or the longest illustrated in this particular database.

The other thing that is interesting here in this well-selected group of patients is they have exactly 7 percent of men on this plot with a doubling time less than 3 months exactly the same as Bill Catalona's.

It sort of shows you that as you go from a

community database, where all comers come in to a very select institutional database, the proportion of the most unfavorable go down, but nonetheless, to my mind, it is validation that that group does poorly, whether they were screened and they end up there, or that they weren't and they end up there.

So, in summary, in terms of patient selection, what we have here are data from cooperative groups, the RTOG, multi-institutional databases, CaPSURE/CPDR, and Centers of Excellence - Hopkins and the Barnes Jewish where the screening studies were started, showing that doubling time is significantly associated with cancer-specific mortality.

I am staying away purposely from surrogate for the following reason that I will now state. I have discussed surrogacy with many different statisticians. Dr. Rubin is the one who is closest to me who runs statistics at Harvard University. He has pointed out all of the issues, the difference between a clinical surrogate and a statistical surrogate.

I would submit that even if you run a randomized study and you apply Prentice's criteria, and you show it works, it still may not work clinically, and the way that one would get around that is by having multiple measures of surrogacy, things like proportion of treatment effect explained, the PTE model, and multiple studies all showing the same thing, like I just showed for doubling time, that would get us to the point where we need to be.

So, I am staying away from surrogacy, I am saying with associations or prognostic factors for the time being, and the conclusion I would make from the data I just showed you is that the doubling time itself is significantly associated with cancer death whether you have had surgery, radiation, radiation and short-term hormones, or radiation and long-term hormones, and that is just about every treatment you can offer to a man who presents upfront.

So, it covers all the treatment domains, and doubling time less than 3-month group is a

particularly poor prognostic group and represents about 20 percent of men who come from the community where screening is not practiced necessarily, and about 6 to 7 percent of men who come from a screened group.

But the point I am going to make is it doesn't matter how you get there, once you are there, you do poorly whether you were screened or not, because I think that that very short doubling time is reflecting biologic behavior.

So, now we have identified some patients for study. Now, we need some issues from clinical practice and what has been done in this country to decide what the arms of this study are going to be.

So, in the United States for patients with a rising PSA, as Dr. Scher and everybody has said, PSA dictates management, the rate of rise of PSA has been shown to influence when hormonal therapy is used.

Peter Carroll from the CaPSURE database has shown this quite nicely the PSA doubling time or velocity or how quickly the PSA rises is

directly associated with the timing of hormonal therapy. The doctor looks at the PSA going up quickly, the patient looks at it, something is done, and in the community, that something is hormonal therapy.

In academic centers, it can be anything from vaccines to Celebrex, et cetera, on studies, but in the community, which is where we are aiming this, the big picture of what we do in this country, it's hormonal therapy.

Then, a very important piece of information from the Hopkins database where men didn't get hormonal therapy until their bone scan was positive. What is the median time to a positive bone scan following PSA failure in a guy with a very short doubling time - 18 months from the one database that could actually measure it, where hormonal therapy was withheld until the bone scan was positive.

So, there is your next piece of information, and that is what sort of drives people's thinking in the community to start

hormonal therapy. So, the bottom line is that patients with a doubling time less than 3 months are offered hormonal therapy. Whether it has been proven to improve survival or not is not the case here, it is what is done, so I would submit that that is a reasonable control arm.

So, here is the study. The treatment arms would be hormonal therapy plus or minus some systemic therapy in the setting of a doubling time less than 3 months.

Now, what systemic therapy are we going to choose, or even more importantly said, what class of agents are we going to choose? This is where the talk takes another twist.

I would say that Taxotere is the leading contender because it is the drug that has been shown to prolong survival in men with hormone refractory metastatic disease, and the thinking is, well, we will backstep it into earlier states and maybe we will even see more of a benefit.

Maybe we won't see any at all, but that is what studies are for. So, that would be my number

one choice would be docetaxel or Taxotere, but there could be a number of other agents used, but let's be careful here.

I would not recommend an agent that isn't cytocidal for the reasoning I am about to go through with the last part of the talk, which has a whole host of data addressing this issue.

We don't know in the cytostatic agents, or agents that modulate PSA, whether anything I am about to say holds, but in the cytocidal, the ones that kill cancer, as Dr. Scher was sort of alluding to, you kill prostate cancer, the PSA tends to go down in the hormone refractory state, well, that is why I would stick to cytotoxics. I put Taxotere as number one, there could be other agents, but I think they have to be in that class.

So, now the last part which gets to the endpoint of this clinical trial. So, you have a rising PSA patient. You have given me hormonal therapy plus or minus some new cytotoxic, Taxotere or other.

The primary endpoint, the conventional one

would be time to bone metastases. It's the next clinically relevant event that comes along the path, and your secondary endpoints would be time to cancer death and overall death, all-cause death.

I think that is your standard approach, and no one I don't think would argue with that, and it is very reasonable, and this study is being done. Dr. Scher and I have been talking about it. I think Dr. Scher has already got it underway. So, this study is already happening or about to happen.

But PSA, and this is where I am going to sort of focus my last part, you know, what is the evidence, is there any evidence to suggest an association between the nadir level of PSA--and I use 0.2, more than 0.2 as a detectable level, because that is a fairly good consensus across the country--what is the relationship between someone who goes on hormonal therapy, rising PSA, and doesn't get below 0.2?

Is there a relationship between that person and time to cancer-specific death in that setting?

Now, I am going to show you a series of studies that I will argue that there is a significant relationship statistically, and then the last point, clinically.

Here are the databases from which these arguments will be made or evidence will be presented. First, the last one I will show you is the multi-institutional database, the CaPSURE or CPDR contingent. I will start with the single institution databases from New York. Peter Scardino, Bianco, and Howard Scher actually worked on this project. Then, I will show the Harvard and Barnes Jewish single institution experience.

So, here is the New York experience. We had 346 men who underwent surgery. Now, this is interesting because not all of them are bone scan negative at the time of entry, 81 percent. I will address that later. The endpoint they used was time to cancer-specific death, prostate cancer specific mortality following 8 months of hormonal therapy, very bright, because it takes at least--the median is 3 months, which we found and

others, but it can take up to 8 months before your PSA nadirs.

So, you set your time zero at 8 months following the institution of hormonal therapy, so you are not biased. Everybody has had a chance to experience a nadir or not by that point. So, your categorical variable or continuous, however you want to look at it, continuous or categorical, has happened by that point.

The covariates that they looked at in the model was PSA level at the start of hormonal therapy, the pre-hormonal therapy PSA doubling time, the PSA nadir that actually occurred within 8 months of hormonal therapy, and then prostatectomy, T-category Gleason score, and bone scan status positive or negative, and the results are shown here.

The PSA nadir level being undetectable was very significant, as was the PSA level at the time of hormonal therapy, and if they had a pre-treatment PSA doubling time greater than 3 months, they did much better than if they had one

less or equal to 3.

The other factors, factors related to the prostatectomy specimen, bone scan status didn't matter. There were 63 cancer deaths out of the 360 or so patients, and the median survival for patients who never nadired on hormonal therapy was about 5 years, which is again consistent with that 6-year number I gave you before, you are just a little bit further into the picture now, it's short.

This is the data that they have, the slide that Dr. Bianco sent me. That dotted line at the top, this is cancer-specific death, the dotted line at the top is the guys who never nadired and who had a pre-treatment PSA doubling time less than 3 months.

Now, they didn't put numbers at risk on here, but you have essentially got 100 percent deaths in the first decade estimated, but if you go out 5 years, you have got 80 percent of the people gone estimated, okay, because it is always subject to follow up, it's a pretty bad group.

Whereas, the people who died of disease, if they did nadir, is the other dotted line where, when you go out about 5 years, you have got about 15 percent deaths. So, there are still some people dying even if they nadired, and I want to make an important biological or clinical point here.

This is the twist in my mind. If you nadir on hormonal therapy, it doesn't mean you don't have hormone refractory disease, because there are still some people who go on to die even if you nadir on hormonal therapy, 20 percent at 5 years, and double that by the time you get out to 10 years.

But if you don't nadir on hormonal therapy, you damn well have hormone refractory disease because almost everybody is dead within the first decade, and I think that is an important point because it is saying it's like, you know, when we biopsy the prostate, if the biopsy is negative, it doesn't mean they don't have prostate cancer, but if you find it, they do.

The same concept here. I think that the

nadir is an important construct because when it doesn't happen, it is very bad; when it does happen, it is not as bad, but it still can be bad. Now, let's go on a little.

This is the data from Harvard and from Bill Catalona, the Barnes Jewish group. This is doubling time less than 3 months, did they get below 0.2 or not, the same picture as Dr. Bianco, Dr. Scardino, Dr. Scher's data set, same picture. A lot of death if you didn't nadir, almost 100 percent in this case by 7 years, but still some, but not nearly as much if you do nadir.

Then, going ahead, the final study. This is the multi-institutional study from CaPSURE and CPDR, which included 486 men who had surgery, 261 who had radiation. At the time of hormonal therapy, everybody who had a bone scan which was negative.

The endpoint here is the same endpoint that the New York group used, time to cancer-specific mortality following 8 months of hormonal therapy. The covariates are all the same

covariates I just mentioned, and the results are exactly the same with the only exception being that Gleason 8 to 10 came in, but everything else in terms of PSA nadir, pre-treatment PSA doubling time, and the PSA level at the start of hormonal therapy are all significant.

In this study, there were 53 deaths, a little over half of them from prostate cancer, and the hazard ratio adjusted for all of these factors, when you didn't nadir, there was a 20-fold increase in cancer death.

Now, let's look at the actual plots, the graph first. This table is important from a statistical standpoint and a power issue if you were going to design a study in this group. I want you to look at where the events occur.

If you look at doubling time less than 3 months, and you look at the column that says Number of Patients, Number of Prostate Cancer Deaths, you will see that 21 of the cancer deaths occurred in the guys who didn't nadir and had a doubling time less than 3 months; 3 occurred in guys who did

nadir and had a doubling time less than 3 months.

Now, you go across the table and you go from 21 to 23 to 24, you pick up two more events and then one more event, and at the bottom, 3 to 4 to 4, you pick up one more event. What I am saying is that the vast majority of the 28 deaths are in that upper left-hand corner box, the doubling time less than 3, and the PSA nadir greater than 0.2.

The reason why this is important is that if you take a trial and you select people with doubling time less than 9 months or 6 months, you will still see a difference, as I am about to show you, but the difference will be dampened by the fact that almost all of your events are occurring in that enriched population with the shortest doubling times.

My point is just that for a power purpose, as I will show in the next three slides, the selection should be very strict if you really want to get an endpoint quickly.

So, here is the plot now, the one I have been showing you all along from the New York group,

the Harvard, Barnes Jewish group, and here is now the multi-institutional group. This is doubling time less than 3 months, did they nadir or not, the same story, same picture. If they don't nadir, they do terribly, almost everybody is estimated to die within 7 years. If they do nadir, some still die, but not all, not nearly as much.

The number at the bottom, 68 over 224 just tells you the percent of patients, which is 30 percent of men whose doubling time is less than 3 months, going on to hormonal therapy don't get below 0.2, almost a third.

Now, that's in contradistinction to what we think, we put people on hormonal therapy, the PSAs go right down. Well, that is because most of them are not doubling time less than 3 months coming in. Most of them are 6 months or 9 months or 12 months.

So, you will see as you go to the next set of slides, here is doubling time less than 6 months, 25 percent of them don't go down to undetectable levels, and the survival difference

here is still significant, but I want you to remember that the only thing that is driving this big difference is the group of men with a doubling time less than 3 months.

Almost all of the events in this doubling time less than 6 months are coming from that very poor group. The same thing with doubling time less than 9 months. Now, you have got 22 percent of people who don't nadir, all being driven again by that worst cohort.

I don't want you to get fooled here by looking at these big differences in 6- and 9-month plots. You have to know where the numbers are really coming from.

So, we are almost done, 2 slides to go. So, the summary of what I said. In a group of men who come in with a rising PSA that is rapid, a short doubling time, less than 3 months, a third of them, 30 percent of them don't nadir at least in this multi-institutional database and the other ones I showed you, despite hormonal therapy, and in my mind, given how quickly and how vastly they all

die of cancer when you look at those cumulative incidence plots, they have to have some component of hormone-resistant prostate cancer in them. I can't imagine that they don't. So, that is Point 1.

Now we come to the study hormones plus or minus Taxotere, and the question is if a guy doesn't nadir to less than 0.2 on hormonal therapy and docetaxel, what does that say? We know that docetaxel doesn't decrease testosterone levels. That has been shown by William Ohe and others in studies of neoadjuvant Taxotere Phase II studies prior to surgery.

So, it doesn't go through that mechanism, and when PSA does go down, it has been suggested from the hormone refractory state that at least there is some association with that in cancer killing or cancer death. That led to a survival benefit, but there was a disconnect between a PSA reduction of 50 percent and survival. Why? Well, perhaps you don't have the ability here of zero, the nadir.

See, in the hormone refractory state, you get down to 4 or 10, you are happy, but here, you are going to either be undetectable or not. So, if you don't go to undetectable levels on hormonal therapy and docetaxel, I would submit--and this is a hypothesis, but I think it's a darn good one--that you are hormone resistant and you are Taxotere resistant, and in my mind, that means you are dead from prostate cancer because there is nothing else that we know works, so I think that is a good endpoint.

That is my opinion, but that is a discussion that we can have. So, the trial that I would then project to you is that if you nadir above 0.2, 30 percent of the time on hormonal therapy, and you could show that that goes down to 10 percent or less on hormones and docetaxel, would that be likely to delay your time to distant metastasis, would that be likely to delay your time to cancer death?

That is a question, I can't answer it. I could guess. I think the answer probably is yes,

but I don't have that. That is the first question here. Then, the second question is in the setting of a Phase III randomized trial, if the proportion of men who didn't nadir went from 30 percent to less than 10 percent, would this produce a clinical benefit, and the clinical benefits I put below, the time to bone metastases, the time to cancer death. Those are the accepted endpoints in this setting.

The question is, is there a connection between this nadir construct in that trial that I described, not all trials, not all agents, this very specific trial, is there a connection or not?

The only way to answer that scientifically is to do the study powered for a distant metastasis and/or survival, and see. But are we at a point where we already can see?

DR. HUSSAIN: Thank you, Dr. D'Amico.

I want to thank all the speakers for very informative presentations and for sticking to time. I am going to be slightly more lenient than Dr. Martino earlier, and give you a 10-minute break. I would like us to assemble at 3:10 if you don't

mind, so we can begin to dissect all of the information that we heard.

Hopefully, we will have a robust, lively, but most importantly, productive conversation where we would come out with some plans. Thank you.

[Break.]

DR. HUSSAIN: Before the committee discusses some of the issues that came up, I would like to begin this session of open public hearing. Prior to inviting members of the public to make their statements, I would like to read this statement.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the 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 any company or any group that is likely to be impacted by the topic of this meeting.

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

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

Also, those of you from the public who have not signed up to speak, you will be allowed to speak after the registered members have already done that. Thank you.

Open Public Hearing

MS. CLIFFORD: Our first speaker is John Willey.

MR. WILLEY: My name is John Willey. I am

the treasurer and board member of the National Prostate Cancer Coalition, which is America's most active group in the fight against prostate cancer.

I speak on behalf of many other prostate cancer survivors, and let me back up for a second. No one paid my way here. I have no financial interest in any drug company unless they are owned by a mutual fund that I am not really going to the second layer of, but I have no financial--I did get a free lunch today, though.

When I was diagnosed with prostate cancer at age 47, there was a lot of problems, and one of the problems, as a baseball fan, was how many more seasons was I going to see. One of the people that I have gotten to know as I have done a lot of work for prostate cancer was Larry Lucano, and as some of you may know, he took over the Boston Red Sox in 2002, and they came on to win the World Series after years of frustration this last year.

I would submit to you that three years would be a real good time for drug approval, that that is something that we should really shoot for.

To get there, surrogate endpoints is the only way to go.

We are dragging our heels on this. I look back on the June meeting and I am wondering what has happened from June to here. We really need desperately to get something moving on surrogate endpoints.

As you know, there are over 2 million men who are now suffering from prostate cancer, and about 1 in 6 men will be diagnosed with prostate cancer. Vietnam veterans, such as myself, have an added higher incidence, about twice the national average.

Prostate cancer gets about 17 percent of the diagnosis of non-skin cancers, and yet has only about 7 percent of the funding for research. We desperately need surrogate markers in place to get new drugs in place. Without the new drugs, we are not going to have any sort of pushing back of this disease, so that it is a chronic, treatable disease.

I have been on a vaccine GVAX, and that is

only in a clinical trial and I received it twice, in '98 and '99, but that alone has kept me going. We need multiple of these types of drugs that can push back prostate cancer and put it into a chronic state, so that men can live with this and die of other causes.

Thank you for your time.

DR. HUSSAIN: Thank you, Mr. Willey.

Are there any other members of the public that wish to speak?

[No response.]

DR. HUSSAIN: I think that concludes our open public session.

Committee Discussion

DR. HUSSAIN: In preparation for the discussion, I wanted to sort of summarize some of the points that were made by the speakers. Then, I would like to ask the FDA for points of clarification on some issues of approval, and then we will go into the questions. The speakers can correct me if my summary is not in spirit with what they have said.

The first thing I think what I heard from everyone, that survival certainly is the gold standard, whether it is practical or not practical to reach, but clearly that is the key.

In the era of active agents, at least in the advanced setting, it is not an impossible goal to get, so unlike previously, where we didn't have good drugs, the problem is not so much the disease, it is really not having active agents.

What you also heard that there are multiple states of the disease to address different endpoints for drug approvals, and that each state would need to be addressed in a separate way.

There are some potential PSA kinetics that might be promising, and I underline promising, because they clearly have not been shown and validated prospectively, but that they are promising and, in fact, will need or may need to be prospectively validated, and that each of these points should be defined in light of the therapy that has been utilized, that one cannot use a one-size-fits-all for these endpoints.

That integrations of other disease-related outcomes are important and should not be excluded, and it should be perhaps included as part of a composite benefit endpoint.

Is that pretty much within the spirit of what you all said? Okay.

Now, I want to just address a few points to the FDA, Drs. Pazdur or Temple, or any of the group. Does an accelerated approval require a Phase III trial? In my experience over the last year, there have been presentations of drugs where they have been approved based on some good results in a large Phase II trial. I just want a clarification on that, so that will help us in our discussion.

DR. PAZDUR: Here again, let's distinguish what accelerated approval is. It's an effect on a surrogate endpoint reasonably likely to predict clinical benefit, and it has to be an improvement over existing therapy or available therapy I should say.

Now, there has been a lot of I think

confusion in the oncology community between accelerated approval and using a single-arm trial for accelerated approval. When you are using a single-arm trial generally, you have to perform the trial in a very refractory disease population, because the comparison is usually to a situation where we are saying that there is no existing therapy, hence, you could use a single-arm trial since the control is recognized as having--there is no control basically, there is no available therapy, so any improvement would be considered an improvement, or "any" in quotations.

The issue here is yes, we would be happy to look at other stages of disease and have a randomized trial. We have advocated doing randomized trials and doing interim analysis looking at surrogate endpoints of response rate of time to progression, and granting accelerated approval on that, and continuing the study on to demonstrate clinical benefit of survival.

That was one of the initial trials that we did was the initial approval of oxaliplatin, 5-FU

and oxaliplatin in colon cancer was a randomized trial initially approved on response rate and time to progression in a randomized trial, but here again, you have to be better on that surrogate endpoint than the control arm.

So, there is various ways of doing it. The major issue is the surrogate has to be in a clinical estimation reasonably likely to predict clinical benefit, and you have to demonstrate to us convincingly that it is an improvement over available therapy.

We have even in some discussions looked at improvements in terms of toxicity or safety being a benefit rather than efficacy.

DR. HUSSAIN: Just so that I understand, so in a third line setting, for example, if you argue that Taxotere is first line, and mitoxantrone for the sake of discussion is second line, someone comes up with a 100-patient trial that shows some composite benefit of palliation, what looks like in the PSA activity, may be measurable to these activities, stabilization and maybe some quality of

life, would that, in fact, make it for the possibility of an accelerated approval in third line setting pending appropriate trials to be done?

DR. TEMPLE: The trouble is you have quoted a lot of different kinds of endpoints. The principal endpoint that we have relied on in single-arm studies has been tumor response, the contention being that tumor responses are unusual, to say the least, in the absence of therapy, so if you see a tumor response, it probably can be attributed to the drug.

We would not say the same thing about palliative responses or improvements in pain. You really do, we would say, need a control group there. So, that is not as satisfactory. Whether PSA convinces you, that is what you are going to talk about.

DR. PAZDUR: The point also is that those endpoints that you specified are truly clinical benefit endpoints of pain benefit, so they would be looked at potentially as full clinical benefit.

DR. EISENBERGER: I do believe that, in

general, for cytotoxics, a clinical trial that would set the bar at survival is still a reasonable thing, but I would suggest also that as we progress with our targeted approaches, that we actually consider paradigms that would have a clinical meaning, such as a bone-targeted approach, for instance.

If you delay the onset or progression of a composite, similar to the Zometa, so that these paradigms be considered, and these are disease-specific, but also treatment-specific, then, they perhaps have a different consideration.

DR. PAZDUR: I think, generally speaking, we would not have a problem with that. Again, we are looking always at a risk-benefit relationship here, and if there is a more favorable toxicity profile, I think there could be an argument made for a delay in a certain event happening. We did this, for example, with the bisphosphonates.

DR. EISENBERGER: For instance, an example is a trial that would build on the efficacy or the primers that were used for the approval of the

bisphosphonate, one would use a radiopharmaceutical and add it to a bisphosphonate, and develop a trial in that fashion, that would have nothing to do with survival, certainly not with PSA, but with the interference with progression of bone target approach.

DR. TEMPLE: But one of the things that would certainly be discussed was whether you have made a change in the person's symptoms of some kind, or whether you have changed a radiologic thing. I am not taking a position, but that would be something that you would have to discuss.

DR. EISENBERGER: Obviously, the trials--

DR. HUSSAIN: Excuse me, Dr. Eisenberger, can I please define just some of the ground rules. That way, we don't end up with in a duel and miss the overall discussion here.

So, the ground rules will be that you raise your hand. We will call on you in order to make the point. In order to accommodate as many people to participate, it would be very good to have very brief and clear points, and I would like

us to, those who want to rebuttal a point, again to raise their hand, and in that way we will call on them in order.

The topics that were put for discussion, they are listed in front of you, and the first question, I am going to read it in general, but I am going to try to take the Chair's prerogative and maybe improvise the way we look at it.

The question reads or the point of discussion reads: Regulations allow granting regular or accelerated approval to a drug after demonstration of safety and efficacy. Considering these two situations, discuss the clinical states in which PSA-based endpoints should be evaluated for use in clinical trials to provide evidence to support either type of drug approval.

Based on what we heard today, there is clearly I think two general distinct states that we probably should focus on, and not get into too many breakdowns.

There is the early stage disease which Dr. D'Amico was pointing to. I would like to reserve

that for the second part of the discussion. But the first part would be metastatic conventional hormone refractory state of disease i would like us to focus the questions on.

In your comments, please phrase whether you believe PSA by itself or some other composite endpoint is what you think is needed.

Anybody wants to begin? Dr. Brawley, we will call on you.

DR. BRAWLEY: Thank you. I was very impressed with all the speakers this afternoon. I will tell you my prejudice right now is Howard Scher had a slide that said that PSA plus other endpoints is one point. That might be a reasonable thing to look at as an endpoint.

PSA by itself clearly is not a good surrogate endpoint except for the one state of PSA rising is a bad thing clearly.

DR. HUSSAIN: Dr. Klein.

DR. KLEIN: I would like to disagree a little bit with Otis. I think there is substantial evidence in the urologic literature, although not

all of it is as rigorous as defined by the Prentice criteria, that PSA doubling time or another form or another derivative of PSA kinetics really reflects the biology of the disease, and Anthony showed a lot of it, but there is more.

There is evidence in the pre-diagnosis, pre-prostatectomy model that a rapid PSA doubling time is associated with poor survival despite aggressive therapy.

There is evidence that Anthony has fleshed out that after treatment, that it is associated after radiation or surgery, there is evidence in the older literature and in the JAMA article that was published multi-institutional study last year by Andrew Stevenson, that in response to predicting a response to radiation therapy, that it is predictive, and all of those things are based on PSA doubling time or some derivative of PSA kinetics.

When you see a predictor like that, that crosses the boundaries of all the different clinical states, it says to me that it is capturing

the essence of the biology of the disease, and we ought not ignore that.

I would agree with Dr. Scher's point that he showed with those two cases, that PSA doubling time is not going to be the perfect surrogate for every case. You will always find exceptions. But we are in a situation now where we have a clear need for new drugs in the management of all these different states in prostate cancer.

Neither pharma nor big academic centers are going to put a lot of time, effort, and money into looking at survival when the survival endpoints are so far off, and it really is time now to design the clinical trials as has been suggested with a PSA kinetic-based endpoint to try and validate it, and whether that will be sufficient for accelerated approval or not, I don't know.

But if we don't do that, we are going to be stuck, and I would just sort of add that we may not as a group today agree on what the appropriate PSA endpoint is, but we should go where the bulk of the data is, which I think supports PSA doubling

time as an appropriate surrogate to test in clinical trials, and then we can have some data and say yes or no, this was the right thing to do.

DR. HUSSAIN: I just want to point out and remind you, please, we are talking strictly right now about metastatic hormone refractory disease, so if you don't mind limiting your comments to that, and then we will get to the early stage disease.

Dr. Andriole, did you have your hand up?

DR. ANDRIOLE: Yes, I did. We are talking about the later stage of patients with hormone response disease, and my question or thought to the medical oncologists, which I am not, is it feasible to do a study in which men with this stage of disease are blinded to their PSA, and just treat them and make your treatment decisions on the basis of symptoms?

Number 1. The first question, is it ethical, and number 2, were it to be considered ethical, would it be doable, because if you could, that would I think give us a lot to talk about.

DR. HUSSAIN: I would probably respond

simply by saying no, I don't think it's doable. Ethical, we can debate it later, but I think doable is more important than ethical.

Dr. Scher.

DR. SCHER: I think what we have seen about PSA doubling time is that it becomes an important prognostic factor as to who is at high risk for a significant event, and that has to be distinguished from a treatment predictive factor, which is a post-intervention outcome.

What we have seen across the states is that this has become critical to identify patients for enrollment, but that does not tell you anything about its role as a potential outcome measure.

DR. HUSSAIN: Dr. Martino.

DR. MARTINO: At the risk of being simple, ladies and gentlemen, I need to ask a question, and I would like a simple answer from somebody, because you are all rattling on, as best as I can judge right now. I want to focus the group on people with metastatic disease, not early disease, metastatic disease. I think that was the point

that you were taking us to.

Is a change in PSA alone, is a change in PSA alone adequate for any of you to change therapy? To me, that is really the question. That's the question, and I would like an answer to that. Is PSA alone adequate?

DR. HUSSAIN: Dr. Brawley, do you want to take that?

DR. BRAWLEY: Yes. First off, Eric, I agree with everything you said for localized disease, but in the case of metastatic disease, I do believe--well, first off, if you give Taxotere and measure PSA several days later, you will have an increase in PSA because of tumor dying out and releasing PSA.

But a sustained increase in PSA, while one is getting cytotoxic chemotherapy, to me does mean progression of disease. A decline in PSA is not nearly as much information to me as a rise in PSA.

DR. HUSSAIN: Dr. Scher, you wanted to respond to that?

DR. SCHER: If the PSA is going up, and is

not affected in any way by a cytotoxic agent, that is a indication that it does not work.

I would add that there are, for example, using weekly Taxotere, you can see delays in the decline of PSA for upwards of 6 weeks, so that is important information to explain to a patient. What? We agree.

DR. BRAWLEY: We are saying the same thing.

DR. SCHER: We agree, yes. Going down, it's helpful, but it's not the whole story.

DR. HUSSAIN: Dr. Eisenberger.

DR. EISENBERGER: I just want to also, just for the sake of keeping in the record, when you treat patients with Taxotere, and the PSA goes up, it doesn't mean that it has anything to do with Taxotere. It is the disease that is progressing. We actually looked into that in TAX-327.

So, these are patients who are rapidly progressing, who will take a little longer for their PSA to go down, but that doesn't happen very frequently. Most of the time, early rises in PSA

equal progression.

DR. HUSSAIN: Dr. D'Agostino.

DR. D'AGOSTINO: I am not sure I digested all the material on the accelerated approval. If some sponsor gets an accelerated approval based on PSA, they still have to do a clinical study, right? So, in terms of moving the discussion, it seems to me like the PSA analyses that we have seen have more been like baseline as opposed to if you have this, you are in trouble.

The progression, I haven't heard that really said that that leads to anything. But studies that talk about the progression as the Phase III in an accelerated approval, and then followed in the Phase IV with a harder endpoint, and the confirmation of the PSA rising, I think would be a sort of a scenario that one could possibly implement without running into some big ethical problems.

But I haven't seen, just to iterate, I haven't seen the increase, the doubling of the PSA as being an indicator of mortality in the data that

I have seen presented.

DR. HUSSAIN: Dr. Raghavan.

DR. RAGHAVAN: I would like to come back to answer Dr. Martino's question. So, the answer I think, Silvana, is it depends on the context. I don't think you can predicate management solely on PSA because prostate cancer is a heterogeneous disease.

Now, if you want to do it on averages, that is, on average will I be accurate most of the time, then, you can do it. If a PSA drops 75 percent, most of the time that correlates with a good outcome. If the PSA consistently rises over a period of 3 months, most of the time that correlates with a bad outcome.

But there are some phenomena that interfere with the answers that we have heard before. For example, there are quite clear data that show that for a number of cytotoxics, if you are silly enough to do daily PSAs, which very few people do, you will identify a flare-up reaction with release of PSA in response to a cytotoxic,

much as you occasionally do in breast cancer with one of the breast markers.

Many of the clinical trials that we talk about sample PSA values at weekly or 3-weekly intervals, so they don't actually have the data to answer the question.

The second phenomenon is a clinical one, which is you will see patients who have a clone that produces PSA that disappears during chemotherapy with a resistant clone that is silent, sometimes neuroendocrine, sometimes not, where you will have a patient who is actually deteriorating, losing weight, losing performance status, increasing pain. So, this is the disconnect between symptoms and PSA when the PSA goes down.

So, the answer to your question is it depends on what proportion of the time you are prepared to accept being right or wrong.

DR. HUSSAIN: Dr. Martino.

DR. MARTINO: So, can I then conclude that PSA alone would not be an adequate way to power a trial, that something beyond that must be added?

If that is correct, then, can we move on a little? What would be the other things that would need to be added?

DR. HUSSAIN: Dr. Klein.

DR. KLEIN: You are correct, you are correct. I mean I would point out again that we are looking for a surrogate that describes or predicts the behavior of a population, not the individual exceptions. No surrogate is going to perfectly predict the outcome for an individual patient, and we need not to perseverate on that issue. I think we need to move beyond that.

I think what you have heard today from everybody is that there is a substantial amount of evidence that suggests that a PSA derivative may be a useful surrogate, but it needs to be tested in a prospective clinical trial, using a standard clinical endpoint, before we will accept that.

DR. HUSSAIN: Dr. Temple.

DR. TEMPLE: It just seems we are saying that PSA isn't an absolute thing, there are a variety of measurements that have already been

discussed, like doubling time or percent reduction, or something, so that you might not be convinced that any change means something, but you might be convinced that some kind of change, a nadir less than 0.2 or something means something.

Can I just say something about possible study designs? It is always tempting to take a look at the people who have a response, like whose PSA goes to something very low, and then see how they do compared to people who don't get that response.

This has been done for years, and it always gets the same criticism that maybe this is true true unrelated, you might have picked out the people with a good prognosis because they are the ones who responded.

There is a study design that I want to throw out, so you can tell me it's impossible, that avoids that problem. If I understood the slides I saw, you can expect a reasonable percentage of whatever PSA response you are going to get in about 6 weeks. It would therefore be possible to take a

population, treat them all, look at what happened at 6 weeks, and then stratify according to response, you know, 50 percent, 40 percent, whatever people thought was meaningful, stratify and randomize to treatment and no treatment.

You do that, and you see a better response, you see a better outcome on whatever it is you are measuring, associated with a bigger PSA response, and then you don't have to worry about Prentice anymore, because if you saw that, that would make it a credible surrogate for outcome, I think.

Now, the obvious question is would anybody let you do that trial. Everybody would be on whatever hormonal therapy there be, but you would have to take people who had a response that at least some people believe in and not give them the drug. So, it would be nicer if you could do some scan at one day or something, and people would be more comfortable with that, but I would be interested in what people think about that as a possible design.

It really does avoid the true true unrelated problem.

DR. HUSSAIN: Dr. D'Agostino.

DR. D'AGOSTINO: Maybe I am not following, but doesn't that sort of stratify by what you think might be severity as opposed to saying PSA is progression after you have taken the drug is going to be useful?

DR. TEMPLE: Well, you are going to look and see, I mean you may also stratify by the pre-treatment doubling time or something like that, but, no, you are taking--let's make it up.

Let's say you want people who fall to less than 0.2, that is one stratum. Less than 0.4 is another, no response is another. We will have 3 strata. Then, you randomize to the treatment or no treatment, and you show presumably that people who had no response don't get any benefit on whatever it is you are measuring, but the people who were knocked down to 0.2 by the treatment have a dramatic improvement in outcome.

DR. D'AGOSTINO: I am missing. When do

you stratify, do you put them on treatment, wait until they respond?

DR. TEMPLE: Everybody goes on treatment. You look at the response and then you stratify. You stratify by response.

DR. D'AGOSTINO: But you have the individuals. I thought you said you looked at doubling and then you categorized individuals, then randomized within those categories.

DR. TEMPLE: That's right.

DR. D'AGOSTINO: Well, they don't have treatment before you randomize.

DR. TEMPLE: They have all been treated for 6 weeks.

DR. D'AGOSTINO: They have all been treated for 6 weeks.

DR. TEMPLE: For 6 weeks or 4 weeks, or whatever you think is long enough to know what their PSA response is. You then randomize them to treatment and no treatment. So, you have got to hope the 4 weeks of treatment doesn't make too big a difference. If it did, that would undermine this

design.

You then have groups who are stratified by response, and you then randomize to the two treatments. So, it is multiple randomized trials in people with different responses. Now, whether you can do that or not, I don't know, but I think it does have the potential for answering the question whether the PSA response, in fact, predicts an effect of therapy on some other kind of outcome, like death.

DR. D'AGOSTINO: But your outcome would be death?

DR. TEMPLE: Well, you choose the outcome. Time to progression, I mean I am not trying to choose the outcome, one that you feel is a comfortable outcome. Could be time to bone mets or whatever you want really.

DR. HUSSAIN: Dr. Raghavan.

DR. RAGHAVAN: So, this is a composite answer to a composite endpoint. This is Dr. Eisenberger and myself muttering together. So, if we understood you correctly, and the randomization

comes in patients who have had a PSA response, it goes back to what Dr. Hussain said. It is not doable in the world today, because patients are so PSA dependent, irrespective of what oncologists think. Most urologists, as you heard earlier, believe in PSA, and get excited about the concept that it correlates with the disease.

So, if you have a patient with metastatic disease, in the early part of their PSA-associated lives, PSA is very important as a parameter of what is going on. It becomes less important later, but they have been trained to be PSA responsive.

So, to say to a patient whose PSA has disappeared, well, we are going to flip a coin, and on the toss of a coin, you might not get that treatment that is about to save your life, has no chance of working. So, you will get an accrual of zero.

DR. TEMPLE: Well, not if they can't get the drug any other way, they won't.

DR. HUSSAIN: Dr. Perry.

DR. PERRY: I apologize. I feel like a

nickel among dimes here, listening to all the experts on prostate cancer. Perhaps you could answer a simple question for me. Everyone wants to compare PSA against a hard endpoint, and I don't know what that hard endpoint is.

I hear you say that survival doesn't work because too many people die of comorbid diseases, and it takes too long. it is the ultimate great endpoint, but for practical purposes it isn't going to work. Time to progression is complicated, and bone scans don't work.

So, what are we going to compare PSA against in these trials?

DR. HUSSAIN: Dr. Perry, I think that in the hormone refractory setting, I think patients, 9 out of 10, of they were going to die, they are going to die from their cancer, so that is not a problem there.

DR. PERRY: It's going to take a long time.

DR. HUSSAIN: Dr. Perry, the median survival in a hormone refractory patient--and

perhaps that is where this whole thing seems to be sort of, if I want to say, oxymoronish in some ways--in the late stage disease, I don't think we have too much of a problem of time way and beyond any other solid tumor.

The median survival of your best patient population that go into chemotherapy trials is a year and a half, that is how good we are, this is it, a year and a half. So, I guess in my mind, the hormone refractory setting in front line, if I may just put my two cents in there, to me, the answer is clear. It's survival endpoints, get drugs up there and randomize and get it done with.

Where I think--and perhaps if we can maybe just to get focused a little bit--if we can agree, for example, that in a front line setting, survival should still be front line for brand-new metastatic hormone refractory disease, that survival is the endpoint because these trials are not difficult to do from time points.

It is more in terms of patient accrual into the trial, and I think we have demonstrated in

the last 5 to 10 years that we have really maximized per year our ability to get these patients in to do trials in a short period of time.

Where I think there may be room to get drugs more into these patients is in the second and third line setting where now that we have Taxotere front line, but it is not exactly curing patients, so the question is can we envision trial designs that are short of being randomized 700-patient trials, that would allow us to test some promising agents in that setting and give us some expedited drugs into the market while we prove the principle.

If I may ask that we focus on that point perhaps, because as I am speaking, I see everyone shaking their head that they are agreeing that, without even a vote, that survival for front line hormone refractory is a done deal, so let's just move on.

The question is we have a second line or third line setting, whatever you want to argue it, can anyone make a recommendation for what they view as a trial design that would be of value? Since

there are people who have raised their hand prior to that, Dr. McShane, I am going to allow her to go first.

DR. McSHANE: Some of the points I was going to raise have already been raised, but I would like to emphasize that to really establish something as a surrogate, no matter what setting we are talking about, it takes more than a single trial.

You have to demonstrate that repeatedly, over multiple trials, that the answer you get on the definitive endpoint is the same as the answer you get on the surrogate, so I think we need to keep that in mind.

DR. HUSSAIN: So, is what you are saying that from everything you heard, that PSA, as it stands right now, with all the suggestions about its correlation to outcome, is not yet a valid endpoint to be trusted 100 percent until we validate it?

DR. McSHANE: That would be my opinion.

DR. HUSSAIN: Just so that people know,

the two randomized Phase III trials that Dr. Alison point out to, the CLGB and the SWOG trial that is going to look at Taxotere, Atrasentan versus Taxotere, there are built into it prospectively criteria to validate the observations that were made in the TAX-3 trial, and then the SWOG-9916 trial, so some validation on percent decline of PSA is being built into these trials prospectively, and this may, in fact, serve as a model for cytotoxic chemotherapy for screening.

Dr. Eisenberger had his hand first.

DR. EISENBERGER: I just wanted to go back on the PSA. I think we are trashing too much the PSA. The PSA, in fact, is used in clinical practice extensively. If a PSA is going down, we know the patients are being helped, if the PSA is going up, it's actually most likely not being effective, and that is what we use.

We effectively use PSA to define whether a therapeutic regimen in the Phase II setting is going to be effective or not, and regardless of whether we agree exactly on how much and for how

long the PSA declines, this was done in the docetaxel regimens, and this is how we eventually defined in two, Phase III trials that there is a survival advantage.

So, I don't think there is a question that the changes in PSA sort of tell us whether a therapy is working or not, and here is the difficulties. When we are actually trying to pin this down and look at a surrogacy for any survival or any other outcome, this is where there is a problem.

Part of the problem is that you can't do a trial when the PSA is going down, and then stop therapy in a substantial proportion of these men, and you cannot continue a trial if your PSA is going up, if this is what you design, just to test the PSA, I think it would be a waste or it would be very difficult to do, and that is why I think it would be a waste of resources.

But one of the things that I wanted to refocus here, what we are trying to do here, is we are trying to come up with a reasonable hypothesis

that need to be incorporated into Phase III trials from now on. I don't think it's enough for us to just do a Phase III trial and find out whether there is a survival advantage.

I think what we need to do is we need to come up with trials that will look at survival as the main endpoint, but also test a certain hypothesis, which is reasonable, and I think we ought to focus on that here today, and provide you with something which is clinically relevant and testable in the context of Phase III trials. This is what Anthony tried to do and this is what Howard tried to do, and maybe we ought to focus on that.

DR. HUSSAIN: I will get back with you as the first person to make a hypothesis once I get the other individuals to speak, so get prepared.

Dr. D'Amico.

DR. D'AMICO: I just wanted to just highlight a point that has been made, and that has been made by several people. In the two, Phase III randomized studies in hormone refractory metastatic disease that we have heard about today, the SWOG

and the TAX-327 study, they accrued somewhere between 700 and 1,000 patients in a year and a half, and then they had follow-up, and they were published four years after accrual started.

So, I want you to think about if we had a surrogate in that setting that was based on PSA, that you could figure out within 3 months after treatment ended, you have a year and a half to accrue, and then after that, another 6 months, let's say, to do your analysis, 6 months to have it peer reviewed and published, when you add all that up, that's 2 1/2 years, so you will buy a year and a half perhaps at best if everything goes exactly perfectly in this setting with the surrogate.

That doesn't mean we shouldn't explore that, a year and a half could be very valuable, but I want people to understand exactly what are we talking about when we are talking about end-stage prostate cancer in a surrogate, we are talking perhaps a year, year and a half sooner to report.

But maybe more importantly, with the studies that have been designed and have this PSA

constructs built into it, we will learn something about the biology. It is conceivable in terms of study design that if these PSA constructs aren't proven to be important, that you can start somebody in a randomized study, they achieve a certain PSA endpoint which you now know is important, and you take them and put them, randomize them onto the next study based on that construct, it is possible that you might then be able to figure out something sooner in the game.

But I just think that the point I want to make is a surrogate in this setting could be of some value, but if you are looking at the most value for a surrogate, clearly, we will talk about it later, in earlier disease would be where that biggest impact could be made.

DR. HUSSAIN: Dr. Grillo-Lopez.

DR. GRILLO-LOPEZ: Thank you. I wanted to make two comments. First, I certainly don't agree that overall survival should be the gold standard even for front line in the setting that we are discussing, and if you look at one of the studies

that has been discussed, presented a couple of times today, the docetaxel versus mitoxantrone study, and you see that the median survival was reached in 16 to 18 months, that means that half of the patients had progressed and died before that, so they probably had received some other therapies.

So, not only the median, but the rest of that Kaplan-Meier curve was affected depending on what other therapies plus a number of other confounding factors those patients had. Overall survival is not a good endpoint even in this setting.

The second point I wanted to make is that, again, searching for focus in this meeting, from what I hear the FDA saying, and from the content of the agenda, I think that the FDA is really looking for recommendations for surrogate endpoints that could be helpful to the FDA in getting their job done, and certainly helpful to pharmaceutical industry in getting these products approved faster.

I also hear that some of the studies, the large randomized trials that are necessary to

validate the endpoints may take 4 to 10 years. That was the comment from one of the speakers.

So, if we were to say that today, we cannot recommend to the FDA a surrogate endpoint, and that we have to wait 4 to 10 years, that means that pharmaceutical companies can really not negotiate with the FDA for another 10 years or 4 years to start a trial, which would then take another 4 years to complete.

So, we are saying that at the earliest, if that happens, we would not be doing trials based on or we would not be completing trials based on surrogate endpoints for another 8 to 20 years.

So, we need to take some risk. We around the table today need to take some risk and say with what we know today, which may not be perfect, which may not be 100 percent validated, is there some surrogate endpoint, PSA, PSADT, whatever, that can be used today while we take those 10 years to validate all of this with 100 percent certainty.

DR. HUSSAIN: Dr. Temple.

DR. TEMPLE: A point you have made several

times now is that if you take people who are hormone refractory, we are talking about much shorter periods of time, so don't make it 10 years right away.

The other thing is that I think Dr. D'Amico's data on initial therapy show unequivocally that if you put the right people into the trials, namely, people with short doubling times, you can do a study very rapidly, and if you put the wrong people into the trial, you have no chance of ever finding anything, because there are not going to be any deaths.

So, that was too discouraging, I think. There are ways to do these even if mortality is the endpoint, but we have never said that mortality is the only endpoint, and if you look at the approvals there have been, they used other endpoints which occur earlier than mortality.

Can I ask Dr. D'Amico a question? Even though people are critical of studies that show the relationship between outcome and the results on a test, a potential surrogate because it might be

confounded, that is the thing you start with. I mean there has to be a relationship between outcome and the putative surrogate in an after-the-fact way, or you don't have a chance.

So, my question for you is, have you looked at nadir, say, as a good candidate endpoint, corrected for baseline doubling time, because in a lot of the data you showed, the two were going together, but one of those is a characteristic of the tumor, has nothing to do with treatment, but the nadir does have to do with treatment, so can you tease out the nadir effect and relate that to outcome?

Maybe you have already done that, because you would expect that at a minimum, even if you weren't entirely satisfied with that approach, it is still what you would expect.

DR. D'AMICO: I will say it quickly because it really doesn't apply to metastatic disease as far as I know, because I haven't looked at it in metastatic disease.

DR. HUSSAIN: Thank you, Dr. D'Amico.

DR. D'AMICO: The answer is they are independent, because they are both significant in a multivariable analysis.

DR. HUSSAIN: Dr. DeGruttola.

DR. DeGRUTTOLA: I wanted to return a little bit to the topic of validating surrogates, and I think an important point here is that the goal of the surrogate is to know that the effect of treatment on the surrogate predicts the effect of treatment on the clinical endpoint, and there is a number of ways to do that, as Dr. Temple mentioned. The design that he proposed is an elegant one, but obviously is only workable when there is uncertainty about the surrogate, so that people will accept the idea of being randomized even if they had a surrogate response.

The other approach is just to collect information from a number of trials and show that you can actually predict the extent of treatment benefit from the effect on the surrogate.

A number of people have commented on the Prentice condition, and I think the Prentice

condition is conceptually very useful, the idea that if you have a test on the surrogate, it's a valid test of the clinical endpoint, but I think that operationally, it may not be the best way to try and approach the issue of surrogacy.

First of all, meeting the Prentice condition, which is that the hazard of the clinical endpoint, given the surrogate, is not impacted by the treatment, in other words, once you know the surrogate, the treatment gives no additional information about the risk of the endpoint.

That isn't really necessary to show that something is a good surrogate. I mean in a case of using HIV viral load in AIDS, no one has ever demonstrated, in fact, that the Prentice conditions are met. Michael Hughes and colleagues work showed that, in fact, only a relatively modest proportion of treatment effect was explained by HIV, but it still has turned out to be a very good surrogate, as everyone knows from the declining death rates, and so on.

The other thing is that it is not

necessary. It may also not really be sufficient. The problem is that a lot of the analyses that are used, are the so-called showing the proportion of treatment effect explained is close to 1, but those estimates tend to be highly unstable both in terms of large confidence intervals, unless you have really big treatment effects, and also, they are very subject to fluctuations when you include or don't include certain covariates, and so on.

I think that they are useful analyses to do, I think you can learn from them, but I am not sure that that should be the primary way of addressing surrogacy.

The other point that Tom Fleming has made a number of times in print with a number of colleagues is that there is an identifiability issue that if the treatment can have negative effects on the outcome of interest by a different mechanism from the positive effects, you can show that a proportion of treatment effect is quite large, when, in fact, the surrogate isn't explaining most of the benefit.

So, I think that while the Prentice condition is a useful way to think about things, and the proportion of treatment effect explained, are useful analyses, other approaches may be preferable for establishing surrogacy.

DR. HUSSAIN: Dr. Scher.

DR. SCHER: I would just like to try to refocus the discussion a little bit. For the patients who progress on hormones, there are two populations, the first line setting where the median survival is 18 months, maybe a little longer with the stage migration, and the second line setting when you are in the order of 12 to 16 months depending on what you look at.

The response in patients after second line therapy, using PSA criteria, is less than 15 percent. So, it is highly unlikely you are going to see a significant impact on survival.

So, the question I would like to pose is, if you are designing a trial based on survival for the sake of argument, in which you will embed some PSA construct with or without other measures, would

the Agency accept a trial which includes more than one intermediate on which to base an accelerated approval, or are you restricted to declaring one, looking at others?

So, for example, if you put in a trial which has one metric, which is PSA response, a second which is based on a PSA progression, and a third which is based on PSA progression plus clinical progression, if all of those three were proposed in a trial powered on survival, could you do an analysis and not be penalized because you happen to select number one, number two, or number three, as your hypothesis?

DR. PAZDUR: You would probably have to have some decision tree here. The answer is yes, but you would have to prospectively adjust here. There are many trials that have multiple secondary endpoints.

DR. SCHER: But the question is if you are using one of those secondary endpoints as the embedded indication for reasonably likely to predict, while the trial goes on to completion, do

you have to declare one, or conceivably could more than one be looked at?

DR. TEMPLE: You have to preserve your alpha, there would be a debate about it, since those are obviously not completely independent, you have to argue about what the correction would need to be, and just--ask Ralph, he will tell you.

DR. D'AGOSTINO: You are powering it on mortality, you said, right, survival, so I think you could very comfortably run a study like this. It may be overpowered on the surrogates, if anything, and that's okay, but that might be what will happen, and you can protect yourself in terms of alphas, and what have you, because you are going to have such a powerful study on the surrogates, it is the question of do you list the surrogates, do you know the surrogates, are we comfortable enough with the surrogate that we are proposing.

I had another question I wanted to ask, and it goes back to Lisa's in terms of pushing for the surrogate. As a statistician, I would be the last one to say that surrogate variable don't need

careful validation, and what have you, but sometimes the hell with that, and when you have the accelerated approval, the surrogate is reasonably likely to predict a clinical benefit.

If we are talking about situations, second line, and what have you, where you might be able to put together a reasonable study with the surrogate, the proposed surrogate, and then move on to a Phase IV that really has an endpoint--

DR. PAZDUR: Or continuation.

DR. D'AGOSTINO: Phase III, it depends on how long the accrual is. If the accrual is fast, and the mortality, you know, it is going to be a solid one, then, why talk about it at all.

But you don't want to have the study based on the survival as, you know, sort of losing track of the fact that if you can run it fast enough on the survival, then, you can look at the surrogate, and I presume everybody would say that would be a fine study.

I am concerned with the situation when you are talking about the survival is going to take too

long, trying to get these hard endpoints is going to take too long, so can you do something with a reasonably likely surrogate, and then put a more careful study together where you can confirm that surrogate variable.

DR. SCHER: The median time to progression in the TAX-327 and 9916, was on the order of 6 months, and if you are looking at median survival of 18 to 20 months, that is not--

DR. D'AGOSTINO: If you can do it.

DR. SCHER: A progression-based trial, whether it is PSA or PSA response, you would still be saving 18 months to a year, so that is significant.

DR. HUSSAIN: Only because we have a lot of area to cover, I want to ask you to please be brief and make the point.

Dr. Klein, you had your hand up.

DR. KLEIN: I just wanted to add something to what Dr. D'Amico observed about a benefit in terms of defining a surrogate and getting the answer 18 months early. That is one benefit for an

individual agent, but there is another benefit. If we can define that surrogate, we can screen other agents a lot more rapidly, and that 18 months is very meaningful in that setting in assessing alternative or new agents. So, there is both benefits.

DR. HUSSAIN: Dr. Raghavan.

DR. RAGHAVAN: I wanted to just respond to Tony Grillo-Lopez's comment, because I think one of the things we haven't stated today, but is implicit, is that there is an awful lot of work going on at the moment with the data that we have already acquired.

So, I know the TAX-327 team are busily playing with numbers, as are the SWOG team and many other people around the world. There is the tool of meta-analysis. So, I think it's a little facile to suggest that if we don't come up with the answer today, we are somehow committing a crime against mankind.

I think the reality of the situation is if I bring a new product to the FDA tomorrow, and we

set up a series of parameters that I embed in my trial, those parameters will have better data available to help evaluate them by the time the study is done.

So, it is not as if, as has been implied now a couple of time, that it is a bad thing to do this in a scientifically rational way. There will be data. Nothing that anybody has said today is going to come out of left field as a surprise.

We know what the current potential surrogates are, and that is why I was making the plea to embed them. I still think, Mike Perry, survival is a good place to anchor this. That was the point I was making.

Where it becomes blunted is if you don't take the state's model into consideration, in other words, survival for someone with early stage disease becomes much more hard to interpret.

DR. HUSSAIN: Dr. Sridhara.

DR. SRIDHARA: I just wanted to go back to Dr. Scher's question of having three sort of PSA-based endpoints and how do we deal with it if

we want to keep all three of them as primary endpoints, and in this case, you are powering the study for overall survival.

I think if you can prioritize which one of them is the first one that you are going to look at, then, probably you don't have to pay a penalty, in other words, if you can go, okay, this is the first one, this is the second one, and this is the third one.

But I think you have to carefully examine the data that is already available, what would be these three, and how would you prioritize. If you think of PSA response and PSA progression, obviously, you will be seeing PSA response before you see the PSA progression.

So, there will be some kind of time effect in your prioritization of how you want to look at it, and whether you want to give higher priority for progression, that may be something that you want to look at, and then we can deal with it statistically. That is not an issue.

DR. HUSSAIN: Dr. D'Agostino.

DR. D'AGOSTINO: If we are talking about the setting where you can do a mortality trial and get it done in a reasonable amount of time, then, putting forth different variations of the surrogate can I think easily be put in, and they probably will have a lot of power.

You can put them in a sequence, as you said, but probably if we are clever enough, we could probably have a reasonably good power on all three of them, three or four, so I think that would be a very sensible type of design.

DR. HUSSAIN: Can we then use that criteria for first line?

DR. SCHER: Yes.

DR. HUSSAIN: Powered for survival and use other endpoints. Howard?

DR. SCHER: Yes. I mean I obviously have a bias toward progression, because I think that PSA response doesn't capture all the information that you can learn, and there is a time factor, but I think if people can start developing trials, and not pay a penalty for selecting one, then, we have

really made significant progress.

DR. SRIDHARA: I think if you can elaborate on how you are going to define this progression, that would be important, like how often are you going to measure this, and how are you going to deal with missing values if it comes.

I think these are the issues that we come up with progression in other solid tumors, when we are trying to measure progression, it is a question of how often you measure, and if you have missing values, how are you going to deal with these missing issues, and those have to be very specific.

DR. HUSSAIN: Let me ask you then a question. Supposing you have drug A you are testing against Taxotere, and drug A wins against Taxotere for a primary endpoint of time to progression by, say, 4 months, and the survival is no different, is that drug not worth it?

DR. PAZDUR: Why? Why isn't the survival, why aren't you winning that survival?

DR. HUSSAIN: If I am God, I will answer it, but I am not.

DR. PAZDUR: I guess the question that I am asking, is it crossover effect, is it inadequate powering of the trial--

DR. SCHER: Or is it a bisphosphonate that doesn't affect survival and affects clinical events.

DR. HUSSAIN: If the drug is brought here, and it has a phenomenal time to progression or progression-free survival benefit, and not a survival advantage, I guess that ties into my question that I was going to ask you, have there been drugs approved based on a progression-free survival?

DR. PAZDUR: Oh, of course.

DR. HUSSAIN: Even though there is no survival advantage?

DR. PAZDUR: Of course, correct.

DR. HUSSAIN: So, a setting like this would not basically kill the drug.

DR. PAZDUR: As long as there is not a decrement in survival.

DR. TEMPLE: We have brought this question

to the committee. There are at least two major reasons why you don't see an effect on survival. One is that people cross over when they progress. That has got to go in the direction of not showing an effect even though you don't know how big it is.

The second is just as a hazard ratio matter, going from 10 to 8 is as bigger effect than going from 20 to 18, so survival is more difficult. It is clearly more difficult especially if it's at some distance from progression.

So, yeah, there are a lot of drugs that have been approved based on progression.

DR. HUSSAIN: Dr. Grillo-Lopez.

DR. GRILLO-LOPEZ: There is two points I would like to make. My friend at the end of the table here, I don't know that anything has been approved on the basis of a meta-analysis as a primary pivotal trial although it is useful in support of certain data.

But more importantly, the word "accelerated" means to be faster than something, in this case, regular approvals, and the more we make

the accelerated approval mechanism similar to the regular approval mechanism, the slower it gets.

So, we tend to discuss randomized trials a lot, and, yes, those are more elegant, perhaps they give you greater security that you are doing the right thing, but the faster way to develop a new agent is with a single-arm trial with the appropriate endpoints, and that is where this committee has to take some risk today and come up with suggestions to the FDA on some appropriate endpoints for those kinds of trials.

I like the situation where Dr. Temple is the optimist and I am the pessimist, because it allows me to make my points more strongly and gives me hope that you are going to act faster in approving drugs.

So, I look at prostate cancer drug approvals, and in the past 24 years, there has been three. It is better than nothing, but it is a dismal record for prostate cancer patients that only three new agents have been approved in 24 years, ladies and gentlemen.

The other thing that I want you to consider is that as you look at the audience here, this is a relatively small audience this afternoon, and if you discount the analysts, the media people, and if you count only the company people, the pharmaceutical company people who are here because they have under development a prostate cancer agent, there are very few of them.

We need to ask ourselves why, why is there not more interest in developing new agents for prostate cancer, and, in part, it may be the hurdles that they have to overcome in getting these agents approved.

DR. TEMPLE: I really must respond. There is no evidence that supports what you are saying. There may just not be any drugs around. We don't know whether it is the difficulty. I really don't think that is fair, and I don't think you should say it.

DR. HUSSAIN: I have to agree with Dr. Temple.

DR. GRILLO-LOPEZ: But he didn't raise his

hand. I need to rebut him, he did not raise his hand. He jumped in and he had interrupted me once before also in the same manner without raising his hand and asking you for a turn.

DR. HUSSAIN: Dr. Temple, please raise your hand.

DR. TEMPLE: Shall I repeat it?

DR. HUSSAIN: You have the floor.

DR. TEMPLE: I just don't think you can say what the reason for the lack of interest in prostate cancer is. I certainly don't know what it is. In fact, if you look at the approvals that there have been, they are not particularly burdensome, they have not required survival for the most part, so I just don't think you can say what you said and know that it's true.

DR. HUSSAIN: Dr. Williams.

DR. WILLIAMS: Your question about time to progression, I think it was a bit abstract in this setting. Yes, we have used time to progression in other settings with solid tumors you can measure.

One of the biggest problems in prostate

cancer is that we don't have time to progression, we have time to PSA mostly because people change therapies, and therefore, we don't, in general, have time to progression, and I think the point could we use time to progression is a bit abstract unless we really develop an endpoint that we can call time to progression, believe there is time to progression, believe it represents what time to progression represents in other settings, and also can measure without 40 to 60 percent missing data.

So, yes, we have done it in other settings, but one of the biggest problems in prostate cancer is we don't have a time to progression endpoint.

DR. HUSSAIN: So, for this part, I am going to take one more response from Dr. Brawley, and then I would like us to go to the next session, and those of you, while Dr. Brawley is speaking, think about what you would like to be hypothesizing to test in the context of a Phase III trial or a Phase II trial for that matter.

Otis.

DR. GRILLO-LOPEZ: Can I ask for a turn, because he has made a statement that I have no basis for what I have said. I have to rebut that.

DR. HUSSAIN: Then, I will give you a moment after Dr. Brawley has done his presentation.

Yes, sir.

DR. BRAWLEY: You actually may want to rebut me, too. I have had the opportunity to do compare and contrast between prostate cancer and breast cancer. Why is it that a number of the very basic fundamental questions in breast cancer, such as does mastectomy or lumpectomy save lives? Why do we have the answer to that, yet, in 2005, we still have an open question is radical prostatectomy better than watchful waiting?

Part of the answer--and it relates directly to this validation of a surrogate endpoint issue--so frequently over the last 30 years, men with gray hair have just wanted to jump to a conclusion, and not be very scientific and not validate surrogate endpoints, and that is why it is really important that we finally get around in this

disease to finally being scientific in doing it.

One of the reasons why no drugs have been developed, and we have studied this issue, as well, is actually the doctor community that treated urologic diseases in the 1970s and 1980s, or especially early '80s, were not very friendly toward randomized clinical trials. They and your patients already knew all the answers, so why do the science.

One of the wonderful things over the last 15 or 20 years is you now start having a number of very sophisticated urologists, some of whom are in this room, like Dr. Klein, who are designing clinical trials.

Now, some of those clinical trials, even today, we are having trouble getting men to go into those clinical trials, so we can finally get the answers. All you have to do is look at all the cooperative group clinical trials in prostate cancer that are not filling up with patients, unfortunately, because so many men know what the answers are now and don't care about their sons

actually getting real answers applied to them as opposed to fake answers.

DR. HUSSAIN: I am going to give you, Dr. Grillo-Lopez, some time to respond, but if you don't mind being brief, so that we can get into the second part, which is what you had been advocating for, is to hypothesize something that we ought to test, so if you don't mind, go ahead.

DR. GRILLO-LOPEZ: Very briefly. I am glad to see the FDA jumping in and commenting every time I say anything, which means that what I am saying is important enough and/or controversial enough to merit a response from them even if they don't raise their hands and ask for a turn.

Secondly, I am on like seven or eight scientific advisory boards. All of them are small companies, but they do have three to five or more new agents that are in clinical trials.

Of all of those, there is only one agent that is going to be studied in prostate cancer, because for a variety of reasons, these companies have been dissuaded from studying their promising

agents in prostate cancer, and that is why they are not here today. Only one of those companies is represented here today.

DR. HUSSAIN: Thank you.

The second point that I think we need to discuss before we go to early stage disease is the issue of the fact that there are several PSA-based endpoints that are possible. We are to discuss the approach to select the endpoints for further study in a prospective clinical trial.

While you are thinking about that, I thought I will summarize what I heard from the first part of the discussion, which was very lively and I think very informative, in that we are all agreeing that survival is good for metastatic hormone refractory disease front line, but we are also willing to entertain the possibility of designing trials with some composite, albeit clinically meaningful, endpoints in trials that are powered for survival--is that a fair estimate--and that whatever PSA exploratory analyses that there are will need to be validated in the planned

prospective Phase III trials.

So, those who are from industry out there, you have your work cut out for you. We need those trials. I had promised that I was going to call on Mario first and then Derek next for the issue of what PSA endpoint to look at or whatever other composite endpoint we want to look at for surrogacy. Mario.

DR. EISENBERGER: I just want to again point out that only recently we had two prospective randomized Phase III trials showing a survival advantage. I think all of us now are very busy looking at the databases and come up with models that represent reasonable hypotheses.

I was gratified to hear that the Agency may be considering approving drugs if you look at different models and different paradigms as long as they are clinically relevant or clinically meaningful.

The question is if you hypothesize something where there isn't agreement that this could be clinically relevant, and the trial is

approved for survival and possible survival and is accrued, if you reach that endpoint early on, even though you don't have survival data, could that constitute reason for an accelerated approval without demonstrating that there is a survival advantage at this point?

DR. PAZDUR: Yes, that is the while purpose of accelerated approval.

DR. HUSSAIN: Yes, that is what we just said.

DR. EISENBERGER: What I did not hear, at this point we don't have a validated model that has shown to correlate with survival, so I am talking about--

DR. PAZDUR: But I think, you know, that would have to be discussed and it is something that we would have to agree with, with the Advisory Committee, et cetera, and this is one of the reasons why we are holding this is, is there an endpoint that is reasonably likely to predict clinical benefit.

Remember, we are not asking for surrogacy

via the Prentice criteria here. Remember our past accelerated approvals, they have been on response rates that are 15 percent, 10 percent, 20 percent, and I think in the oncology world, people could question whether these are true surrogates, but we have accepted these as reasonably likely surrogates.

The other point, we are talking about these endpoints as if they existed in a vacuum, and not having any magnitude to them. For example, if we took an endpoint that was a PSA nadir of a certain value that was predefined, there is a tremendous difference between a drug that produced a 5 percent PSA nadir versus something that had a 90 percent PSA nadir in the population.

So, I think we have to think about that also in making regulatory decisions and also looking at these endpoints that are still yet to be proven. There is a magnitude here that has to be looked at also.

DR. HUSSAIN: Just remember this is your chance to recommend whatever your wish list is of

potential PSA endpoints or other potential endpoints that are to be put forward for the test, so that is exactly what we are talking about here, and I would like us to not go back to what we discussed about approvals and otherwise.

Dr. Raghavan, you are next.

DR. EISENBERGER: Can I just say on TAX-327 at this point we are defining a progression model, you know, censoring was initial, and we are reformatting the database, coming up with a definition of a progression composite that correlates in a multivariate analysis with survival, and that will then be a testable hypothesis for a subsequent Phase III trial, which will be powered for survival.

So, if you reach a reasonable test of that hypothesis, as I understand that could be as long as it's reasonable, the reason for accelerated approval.

DR. PAZDUR: A lot of it depends on the magnitude of change here that we are seeing in that endpoint. One thing that is dangerous about these

composite endpoints that we are talking about, that have PSA as one of the composites, is the whole endpoint may be driven by the PSAs.

You know, if you are taking a look at bone scanning plus PSA, let's face it, that whole endpoint is going to be driven by PSA changes, and we are kind of fooling ourselves by calling it a composite.

DR. HUSSAIN: Dr. Raghavan.

DR. RAGHAVAN: So, I am going to hypothesize and run. I would suggest that we begin to explore strategically for accelerated approval the use of the 3-month PSA 50 percent reduction, and I like Howard Scher's idea of multiple endpoints, so I would add to that a 75 percent absolute PSA reduction.

I would put in the caveat, just to remind everyone of history, Dr. Temple and Dr. Justice were troopers here when I was on ODAC, and we had a very controversial drug that came to us that was fated on two bases, wonderful PSA responses, wonderfully high level of toxicity, and a

pharmaceutical company that had one pivotal trial, and were outraged when we turned them down.

The reality of the situation was that the turndown was based on inferior survival in the test arm, so the divorce of survival from surrogate endpoints shouldn't be allowed to happen, because it is a trap.

I am totally sympathetic to Dr. Grillo-Lopez that companies can go belly-up with new products, but the flip side of that is companies can make a lot of money from good products. I personally don't lose any sleep over the fact that all the drugs that don't work in prostate cancer haven't been approved. I totally agree with Bob Temple, why would we prove ineffective drugs.

So, I would hypothesize that PSA time dependent kinetics are worth exploring, but that that exploration should not be divorced from a standard that we know in hormone refractory disease, which is survival.

DR. HUSSAIN: Just to modify what you

said, or to ask you the question, is it important to bring your PSA down or is it important to bring it down and keep it down?

DR. RAGHAVAN: I would say we need to do both. That is why I like Howard's idea of being flexible. I would bring it down and keep it down, and we have some data from SWOG, preliminary, that suggests a 3-month time point, and I have proposed a 75 percent reduction, and I am not going to fight anyone, if they want to make it 50 percent absolute, that's fine. I just think 75 percent is setting the bar a little higher as we understand it, and I figure that is a good place to start the discussion. But I am going to leave now, so thank you.

DR. HUSSAIN: Dr. D'Agostino, and then Dr. Scher.

DR. D'AGOSTINO: I may be asking out of turn, because I want to go back to the accelerated approval. If it was a mortality study, you have the surrogate, a likely surrogate, you give approval, then, you tell them to continue this

mortality trial. You don't stop and start all over again.

DR. TEMPLE: But, Ralph, that is if the accelerated approval is based on the early phase of a trial that is ongoing.

DR. D'AGOSTINO: Exactly.

DR. TEMPLE: As you know, because they were presented to the Oncology Committee, we have not always done that. Sometimes you have to start a new trial, and that doesn't always happen, et cetera, et cetera.

DR. D'AGOSTINO: No, but this fits in nicely with the way we are talking about a mortality trial with surrogate endpoints built in, and then you can move on.

DR. PAZDUR: And that accelerated approval paradigm is commonly used in AIDS with 6-month viral load reductions going on to 12 months.

DR. HUSSAIN: Dr. Scher.

DR. SCHER: I was just, you know--

DR. HUSSAIN: Oh, you are deferring to someone else? Dr. Temple, sir.

DR. TEMPLE: No, I had a fundamental question. There are now enough data, I would have thought, so that one could start looking among the trials that exist already and look at various candidate surrogates and see, you know, with all the flaws that this after-the-fact stuff has, and see at least whether they predict, so you would be able to say a 50 percent reduction, no, that doesn't tell you anything, 90 percent reduction, that is pretty good, that does predict.

So, there ought to be some way to look at those right now and see which ones are promising candidates. You can tell me I am wrong, but that is where you would usually start.

DR. HUSSAIN: In fact, this is what I was making a comment about. In the SWOG-9916 trial, there is PSA data that has been analyzed. It may turn out that different cutoffs are more in line with the Prentice prediction of a surrogate than others, and that is what is going to go into the prospective validation.

As we speak, the paper has been written,

so the information will be scrutinized and come to publication, but after Dr. Scher speaks, I have a question to the FDA.

When was a response ever validated as a surrogate by all the harsh criteria that we were asked to comply with? Has any disease where you accept response as a measure to approve a drug where a response actually was rigidly, you know, scrutinized for the Prentice criteria or any other criteria?

DR. PAZDUR: Here again, you know the data in prostate cancer, breast cancer, colon cancer. There is a great deal of debate regarding response rates and their even correlation to survival, let alone true surrogacy.

That is why we have used those generally as reasonably likely, and here again, I think when one takes a look at a response rate, you know, you have a number of complete responses, duration, where they occur, are they associated with symptoms. You know, it is a very complicated issue, and it is not just in a vacuum here.

It is a complicated thing and there isn't a lot of data here. You know, they are still arguing about response rate correlation in colon cancer with survival, the area that I am familiar with, and a lot of this has to do with our therapies in the 5-FU era were so meager.

DR. HUSSAIN: Howard.

DR. SCHER: I don't know how specific you would like to be, but I would like to make the argument that there is a durability component that is important to the response duration. Again, looking at the median, I would put the bar at 6 months for the response, whether it's a 50 percent decline.

I would also add the no rise versus rise, because you do see patients who do achieve their nadirs beyond 6 months and some patients who benefit who never achieve a 50 percent nadir. Those patients would be, I would argue, devastated if they were taken off treatment when their PSAs were going down with no other signs of progression.

I was very encouraged by Dr. Sridhara's

comments that we could look at multiple endpoints at the same time and just power the trial based on the one that might occur most distally using a 6- or 9-month time frame.

DR. HUSSAIN: Just for the sake of my summary here, and I don't mean to interrupt you, what was your first proposal?

DR. SCHER: I would add no rise versus rise in PSA.

DR. HUSSAIN: And that is the only proposal that you made?

DR. SCHER: And I would add one that would include as progression, objective measures obviously to be discussed, you know, either clinical deterioration or change in therapy. When we looked at our patients on first line microtubular targeting agents, 120-odd patients were treated, about 85 went on to second line therapy. The median time to administration of a second chemotherapy was 6 months.

So, that is essentially where that is coming from and arguably, the decision to change

chemotherapy would suggest that the patients needed a change in treatment. This wasn't a soft endpoint.

DR. HUSSAIN: Just so that we don't stay all night--unless you want to, and I am happy to stay because I am here until tomorrow--what I wanted to do is not miss the discussion on early stage. I have here Dr. DeGruttola who had his hand up and then Dr. Sandler and then Dr. D'Agostino, and then we will move to the early stage disease.

DR. DeGRUTTOLA: I just want to say briefly in response to the question about are there other diseases in which there was extensive analyses of surrogate that led to changes in FDA policy, and I think AIDS is an example of that with the viral load measure, surrogacy analyses were done.

In addition, it was found that with more potent drugs, you could drive virus below levels of suppression, at which point immunological decline was very much slowed down, in fact, immunologic function definitely improved, and I would think if

it were possible in the prostate setting that some people could be driven to PSA levels where progression is really quite rare, I don't know if that is possible, but that would be sort of comparable to the AIDS setting.

Even if that weren't possible in most patients, but it were possible in some, and in those patients, they didn't progress, progression rates are really low, then, I would think that that would be the kind of evidence that might be developed without needing a whole large range of studies.

DR. HUSSAIN: Dr. Sandler.

DR. SANDLER: My question is were you going to save some time to talk about localized disease, and you answered it, thank you.

DR. HUSSAIN: And I just said yes.

Dr. D'Agostino.

DR. D'AGOSTINO: I just want to make sure that because we are saying you can do three or four endpoints, the surrogate endpoints, that that makes it an easy task. I mean one has to be very careful

about how you do spend your alpha through them.

You don't necessarily just power against the one you think is least likely, so you want to keep us statisticians in business and make sure you visit one.

The other is that when you move to these surrogate endpoints, then, the visit scheduling, and so forth, that we were talking about, becomes very, very important. I mean you are not just asking did the person live or die, you are asking within a month, within a week, and so forth, what is happening, and so it is a whole different level in following these endpoints, and that has to be built into the studies.

DR. HUSSAIN: Thank you. So, if I were to summarize as to what hypotheses on the table to be tested, it is a percent decline of PSA, and it is your wish 50, 75 less or more, at some finite period, percent decline of PSA at 3 months. Dr. Scher suggested no rise versus rise plus some other objective criteria for progression.

Are there any other suggestions or ideas

or thoughts or hypotheses? Okay.

Then, I would like us to spend the rest of the time--and I would want to point out there is one population that we have not gotten to speak about, which I think is very important because there may be a clear answer in it, and that is the non-metastatic androgen-independent patients where potentially time to development of metastases would be a good endpoint in randomized trials, and it will not take a million years to get.

So, if I may sneak this in and put that as a conclusion statement and move into the early stage disease, and open the floor for that. Mario.

DR. EISENBERGER: We don't have enough data to give you a more solid, concrete model, so I would like to ask you the opportunity for maybe in the next three months to provide the data from TAX-327.

DR. PAZDUR: Yes, that would be fine, and here again I want to emphasize one of the reasons why we are having this workshop is an exploration of ideas. This is not the last time that we will

be discussing this whole issue, believe me, and we will be bringing this back and hearing from you and doing other discussions with you before our next ODAC.

DR. HUSSAIN: So, who wants to start the discussion? Dr. Sandler.

DR. SANDLER: Thank you. I think I would first just like to congratulate Anthony D'Amico because I though this presentation was terrific, and the idea of the PSA nadir of 0.2 as being a sign of treatment progression or the hormone refractory state, I think is fascinating.

In terms of localized disease, something relatively uncontroversial, I hope, and that is that for a novel local ablative technique, such as radiation, surgery, cryotherapy, who knows, some new novel local technique, I think that simple biochemical failure is an adequate endpoint for a clinical trial.

I think that has wide acceptance in the community, something that Rick Pazdur mentioned in his introductory remarks, so in my mind, if I am

thinking of a new machine or a new radiation technique, and I define a Phase III study, while I would love to collect data for survival, I think that primary PSA failure is an adequate assessment of the efficacy of the novel technique.

I don't know whether that is worth discussing or not, but I think since some of it may be outside of CDER, but I think it is an important issue nonetheless, especially since it affects how CTEP deals with a lot of prostate cancer clinical trials.

DR. HUSSAIN: Just so that I understand it, and clarify it, that would be applicable to an intervention at the prostate level modality, you are not suggesting that, for example, for radiation and Taxotere, to have a PSA endpoint.

DR. SANDLER: Right. I am thinking of radiation A versus radiation B. Although I think there is data to support the ability to use short-term hormone therapy concurrent with the novel therapy, and still have an adequate PSA endpoint, for example, in the radical prostatectomy

trials where neoadjuvant hormone therapy was used, there is wide acceptance that there is no difference in biochemical failure, and that has affected the way therapy is done in the U.S.

So, I think that a biochemical endpoint, even with short-term hormone therapy, is adequate.

DR. HUSSAIN: Dr. Klein.

DR. KLEIN: Just a follow-up question for Dr. Sandler. There is a lot of controversy over how you define PSA failure for therapies that leave the prostate in situ and I am wondering if you could suggest to us some consensus definition that would be appropriate.

DR. SANDLER: I think that there is a lot of controversy, as you mentioned, in terms of the radiation community as to when you declare someone a failure. If someone really has cancer, they will express it by having an elevated PSA, so the question is not whether they failed or not, but maybe how quickly you can call the failure and how important the failure is.

In the radiation community, we are moving

from the well-used ASTRO definition of three consecutive rises in PSA to a discrete rise of 2 nanograms above the post-therapy nadir. The advantage of that definition is that it probably works for both patients who received hormone therapy and radiation and those who received radiation therapy alone.

I think in the surgery community, there is even some controversy as to when biochemical failure occurs, but if you really have cancer, it doesn't really matter whether you call it a 0.3 or 0.4 or 0.5, it will show up.

DR. HUSSAIN: Dr. Bross.

DR. BROSS: Yes, I am from the Center for Biologics. I would like to thank the gentleman from the open public hearing. He is the only one who has mentioned vaccines so far, and I will say in contrast to the metastatic indication, there are a lot of vaccine studies, and we desperately would appreciate advice from the Advisory Committee in terms of what is the appropriate trial design.

At the moment, we have a number of study

proposals that propose to include patients with a rising PSA, usually PSA doubling time of less than six months, say, and the question is, is this an appropriate endpoint.

Dr. D'Amico suggested less than three months was more associated, and also what is the appropriate trial population, is there a population of patients with rising PSAs and no metastatic disease.

That would be the easiest to study because then you just study the time to development of metastatic disease, and also, what is the appropriate measurement of metastatic disease. We don't usually accept bone scans, but in this case it may be appropriate.

So, we would very much appreciate any advice you can give us with respect to this population.

DR. HUSSAIN: Dr. D'Amico.

DR. D'AMICO: I think it is important that we stay to the topic because we have gone completely away from the rising PSA state just

following surgery or radiation, and, Maha, maybe it would be good for you to phrase the questions that you want us to answer in that particular disease state. Maybe they are the same questions we just did.

DR. HUSSAIN: It's the same question as to the PSA endpoints, but dealing with early stage disease. In early stage disease, I think there are two settings. There is the brand-new patient where you are trying to maximize and/or improve local therapy for with or without systemic treatment or some other modality, and then there is the setting of rising PSA post-local therapy.

Howard began making comments about the first part, and then, of course, there is the rising PSA. If I may make a suggestion, because the bulk of the population that we struggle with is the rising PSA post-local therapy, if you don't mind that we focus on that population, and Dr. Bross raised the question regarding, for example, vaccines in that setting and what kind of trial design, if, Anthony, you want to take that.

DR. D'AMICO: I think in the talk that I gave, I really tried to focus very carefully, because I don't think you can explore all types of drug classes with one study design, and so that the design that I put forth was one in which you take a very unfavorable population, short doubling time.

You can justify hormonal therapy as the conventional treatment, and then you randomize them to the plus or minus a cytocidal agent in which the endpoint and progression is not nadiring.

So, I think that with vaccine therapy, this trial design would not apply necessarily, because--again I am not an expert in vaccines, but my understanding is that whether it's cytocidal or cytostatic is a question.

If it's cytostatic, I don't think you should apply such a design with a nadir construct. If it's cytocidal, you might be able to.

DR. HUSSAIN: If I may just take the Chair's prerogative to make a comment, I am not so sure that the rising PSA population--and I am going to go out on a limb to make that statement--is the

appropriate population for drug discovery, so that if you have vaccines that have not shown evidence of activity in advanced disease, to me it is wrong to bring them into the minimal disease setting trying to prove a point.

So, to me, this population as Anthony suggested, is perhaps a population where we would have some drugs that have shown some evidence of activity in advanced disease in some form of setting, that we know they will have a chance of working, and then bring them into the early setting.

Howard.

DR. SCHER: I will respectfully disagree. I think there are patients within this cohort who have a relatively favorable prognosis, yet, who are extremely concerned about their doubling times and rising PSAs, who do not want to undergo medical or surgical castration, in whom there is an opportunity to explore vaccines.

This is actually in some cases ideal because you have a biomarker. In designing the

trial, I mean I think you can do exploratory studies in patients with modest doubling times, we have selected a year or two as that window.

If you are looking for a patient with a rapid doubling time, that is not the group I would use an experimental untested vaccine, but if you did see some efficacy or some effect on PSA, recognizing it has problems, a design that could be used is a discontinuation design with hormones plus or minus the vaccine.

So, we have actually looked at effects of hormones, and looking at long-term survival, as suggested, there are patients with minimal tumor burdens who may, in fact, be cured with hormones alone, and if you want to integrate cytotoxics, you would have to build on those results.

So, you could then look at what proportion of patients reach a nadir that is undetectable and stay there as one readout depending on the level of effect that you see.

So, I think to try to do this study looking at what is a reasonable endpoint of

objective metastatic regression would be very, very difficult as the PSAs are going up. So, you would have to show some treatment effect first.

DR. HUSSAIN: Dr. Williams.

DR. WILLIAMS: Anthony, I think to clarify your endpoint, because I think I understand it from our earlier discussions, it is a dichotomous endpoint which is measured at a certain length of time after a patient is treated, perhaps 8 months, so at 8 months, the percentage of patients who will have not nadired, that is the endpoint you are suggesting, is that correct?

DR. D'AMICO: That's correct, and the 8 months is important because multiple studies have shown that it can take up to that long for that to occur, and the way the study would be exactly powered is you would use from the data available with hormonal therapy alone, you would know the percent of patients who would achieve progression, that endpoint, not nadiring, and then you would say I would like to see a 10 percent or 15 percent difference.

I think having said that, it would be important that that study looked at that as an endpoint, but that it be powered for time to distant disease, which is your clinically significant endpoint, you know, beyond the rising PSA.

DR. HUSSAIN: Dr. Sandler.

DR. SANDLER: I just wanted to comment about the rising PSA situation after local therapy. Usually, we are talking about rising PSA after surgery.

Now, those patients could have distant disease, but there is a certain subset of patients with a rising PSA after surgery who only have localized disease, so in the design of clinical trials testing new systemic therapy, I think we should be careful to either mandate or allow local therapy, such as radiation, prior to enrollment.

I mean I think that it is potentially unethical to treat a localized prostate cancer patient only with an untested novel systemic therapy.

DR. HUSSAIN: Dr. Martino.

DR. MARTINO: Just a basic question to those of you who deal with this disease. Given a patient who has had local therapy only, a newly-diagnosed patient, be it surgery or radiation plus or minus whatever hormonal therapy you folks like to use, and then you are watching them and their PSA rises, do we actually know that you intervening at a time before there is clinical symptomatology actually alters anything, and what is that something that is altered, is it survival or is it time to clinical event?

DR. HUSSAIN: If I may answer that, and that is, there is no prospective data that has demonstrated an impact of an intervention in a randomized manner, so that is a fact of life.

The history of hormonal therapy in this setting is that over and over again, not necessarily in the rising PSA, but if you look at all the hormonal trials historically, there is an indication potentially that hormone therapy may delay progression.

If you give it adjuvantly, you can prolong life, but no one knows whether you intervene today, when the PSA is 5, versus when the PSA is 100, or when you have metastatic disease, that survival is impacted.

So, that is an unknown, and that is the biggest shame of our community, is that that simple question has not been answered.

DR. MARTINO: Whether it has altered time to clinical symptomatology.

DR. HUSSAIN: Well, clinical symptomatology is a bit late in the process. I think we know it delays metastases. There have been trials looking at early versus delayed hormonal therapy for patients who have either upfront metastatic disease or locally advanced disease, indicating that those who have been treated with hormones have less odds of developing symptomatic disease, that there is more cord compression, bladder outlet obstruction, things of that sort.

Understanding that this is not the case in

this country, patients get treated early when they have metastatic disease, and as you heard from Dr. D'Amico, a fair number of people in the community are treating simply by a rising PSA.

Dr. Scher.

DR. SCHER: We don't have sufficient data in terms of overall survival, but again looking at long-term outcomes, the difference in survival appears to be similar to what you see in breast cancer populations.

So, we have actually looked at the proportion of patients who achieve a nadir of zero post-prostatectomy, and, yes, we included radiation patients, in relation to whether they had minimum metastatic disease and their PSA levels, and not surprisingly, there is an association.

So, why not, with the availability of cytotoxic drugs, why can't we just shift the paradigm to try to make an undetectable PSA as our endpoint, and ideally, if you have an undetectable PSA, and the patient is off hormones, and their testosterone levels are normal or back to their

baseline, arguably, those patients may, in fact, be cured, and I think that is where we should be setting the bar for the patients who have aggressive disease.

DR. HUSSAIN: Dr. Eisenberger.

DR. EISENBERGER: I hear all of the discussions, and I think what we need is to come up with a reasonable set of endpoints other than survival. Survival is not possible. That is ultimately an endpoint where we can validate some of our hypotheses.

I just want to point out that today, we don't know what the long-term effects other than toxicity of early antigen deprivation is for patients with non-metastatic prostate cancer.

The fact is, is that we probably estimated somewhere around 7 out of 10 men today get treated with hormonal therapy before they develop metastatic disease, and that is a measure issue when we talk about designing our clinical trials, unless you blind PSA and do it.

At Hopkins, as you know, there is a

generation difference. In the past, very few patients would actually receive hormonal therapy until the development of studies, there is a current database, about 11 percent of our patients, and 5,000, that Anthony demonstrated, and 900 with high PSA relapsed. Eleven percent received antigen deprivation treatment.

As we update these data, now, about 30-some percent of these patients are now receiving antigen deprivation treatment, so there is at an institution where there is a conservatism in terms of initiating hormonal therapy, and that is changing.

So, I don't know what the endpoint should be, but I think that that is the critical first step before we talk about anything is what, in an adjuvant trial, is bone scan metastasis what we need to use as an endpoint, is it any form of metastasis, is it initiation of therapy using certain parameters? I don't know. I think this is where we need to focus a lot of our discussion.

DR. HUSSAIN: Dr. Brawley and then Dr.

D'Amico.

DR. BRAWLEY: I just want to make a couple of brief comments. These are all related, yet unrelated, as we talk about PSA rise after treatment.

Dr. Catalano recently published a paper that suggests that 30 percent or more of his patients, does a radical prostatectomy on have a rising PSA within five years of the radical.

In the prostate cancer outcome study done by the NCI, for all comers in a large community, a large city, it was nearly 40 percent of people who undergo a radical prostatectomy have a rising PSA afterwards, so the number of individuals who have a rising PSA afterward is a considerable number of individuals.

Many of them do get hormones, which cause osteoporosis, and I have seen patients who have died, not of their prostate cancer, which they were technically cured of, but of a broken hip due to their hormonal therapy.

Also, the prostate cancer prevention trial

data, which Dr. Klein knows probably better than anyone, that study screened a large number of men in their 60s for 7 years and diagnosed 12 percent of those men with prostate cancer due to screening and then said the hell with screening and biopsied everybody who had a normal PSA for 7 years and found that 15 percent of those men had prostate cancer.

So, of this 26, 27 percent of all men in their 60s who have been diagnosed with cancer, the NCI, through Rocky Foyer's [ph] data, indicates that 3 percent of them will die from prostate cancer.

So, with screening, we can diagnose 12 percent of men with prostate cancer, only 1 out of every 4 for whom will ultimately die from the disease, but I worry about the guys who get radicals and have a rising PSA, and that rising PSA is actually not a threat to their life.

So, a survival study using that group of people actually might be fraught with some dangers.

The last thing I want to note is I talked

about the new breed of academic urologists and I forgot to mention Dr. Andriole who is over there.

DR. HUSSAIN: Dr. D'Amico.

DR. D'AMICO: Mario's point that even at Johns Hopkins where hormonal therapy was withheld before a positive bone scan, now went from 11 to 30 percent of people having that, sort of documenting what I said, and that is, even in now academic centers, fastly rising PSAs, people go on hormonal therapy, so I think it justifies that in a control arm of patients with very rapid rises in PSA, i.e., short doubling times.

To Dr. Scher's point, this is an important one. An undetectable PSA, this is really important that you get this, an undetectable PSA, after hormonal therapy following surgery or radiation, does not mean you are in the clear. You can still recur and die of prostate cancer. That is what those curves showed you. Guys who nadired, 15, 20 percent of them still died of prostate cancer, but a detectable PSA is always bad.

So, I am arguing that the endpoint should

not be undetectable, but detectable. It is just the reverse. It talks about the endpoint being a progression endpoint. A statistician would say this is an event, not a non-event, this is an event, don't get undetectable PSA, it's an event, and that is always bad, so I think that that is an important distinction.

To Otis' point, I think your point about people getting hormonal therapy and dying of the side effects of treatment is an important one, osteoporosis, neurocognitive issues, QT, and so on. That is why the long doubling time patients should go on studies with vaccines and things that are not involving a treatment that might impact their longevity, and the short ones, though, don't die of side effects, they die of prostate cancer.

But I have one more thing, Otis, that you will find interesting. The 3 percent number, one-third of people sustain PSA failure, a fifth in the community have a short doubling time. That is one-third times one-fifth is one-fifteenth. That is 6 percent.

I showed you that of the guys with the short doubling time, a third of them don't nadir. One-fifteenth times one-third is one-45th. That is 2 percent, 2 1/2 percent. There is your 3 percent.

So, the people who die from prostate cancer, the 3 percent number can come from PSA failure, short doubling time, don't nadir, that is 3 percent, and I think that's it, and I think it's that simple.

DR. BRAWLEY: I am agreeing with that.

DR. HUSSAIN: Okay, and I am glad we are one big happy family.

Dr. Klein. I am going to probably ask afterwards do we want to wrap it up, or do you have any other burning questions, the FDA? No. Then, I will summarize and then people can object to my summary or agree with it, and we will go from there. Dr. Klein.

DR. KLEIN: So, to focus on the post-treatment rising PSA population due to Dr. D'Amico's work and all the people who collaborated with him, we have more data on PSA as a predictor,

as a surrogate loosely used, than in any other disease state in prostate cancer, and we ought not ignore that.

I would put my vote with the suggestion that PSA doubling time be used as a stratification or selection criteria in this population, and that nadir versus not be used as the response criteria, and at least as an initial pass, and we should move on that quickly. We don't need more preliminary data on this, it has all been done.

DR. HUSSAIN: Dr. Pazdur.

DR. PAZDUR: Here again, you are using it as a prognostic factor. The question that I have, one of the areas that we have looked at is basically in order to verify a surrogate or even a correlate, you have to have an effective therapy in the disease, and that is what enables us now to take a look at hormone refractory disease, because we could look at the Taxotere studies, for example, and we could develop new drugs in that area.

But in this PSA rising situation where you have no therapies that have demonstrated an impact

on a clinical endpoint--

DR. HUSSAIN: Because they have never been tested.

DR. PAZDUR: Okay, but you don't have them, so how can you then verify any surrogate endpoint here, and I guess that is a question for Dr. D'Agostino, can you, in the absence of an effective therapy, really--I am using the word verify loosely, because I don't want to use the word verify a surrogate, but even look at a correlation even.

DR. D'AGOSTINO: Are we talking about where we are going to do a mortality study or some endpoint?

DR. PAZDUR: There is no tie to what you are doing to a clinical endpoint here in this PSA rising, is that what you said--validate it, to validate it.

DR. HUSSAIN: This is the rising PSA, Dr. D'Agostino, where those patients, if you take them as a lump sum, a good number of them are not likely to die from their disease, but as Dr. D'Amico

pointed out, there is a subset based on sort of retrospective PSA data analysis, that you might be able to predict that this is the subset that has a shorter survival.

But I think what Dr. Pazdur is asking, since all of that is retrospective, how are you going to then design a trial with an endpoint that can be reached before we all retire, and validate at the same time whatever hypothesis you have about a doubling time, or a nadir PSA, or any other criteria.

DR. D'AGOSTINO: I think you would have to go back to something like Bob was suggesting earlier, that you try to get a reading on the increase and then randomize things of that nature that you have to be able to sort of set a baseline and then move on.

DR. KLEIN: In this population, I think you would have to use a time to progression endpoint, recognizing the imperfect definition. No one will ever stay on a study long enough or, as Dr. Scher pointed out, detectable versus

undetectable PSA. That triggers additional therapy in the community, and the clinical benefit is no additional therapy.

DR. HUSSAIN: Dr. Scher, you had your hand up a moment ago.

DR. SCHER: I reiterate that I think the undetectable PSA with a normal testosterone is a good start to suggest efficacy. In the minimal disease settings and other tumor types, there is a cure rate, so we can ask the question appropriately using the prognostic models that have been so well described now, and use them in trials.

DR. HUSSAIN: So, let me ask you this, though. That would not apply if the patients have gotten hormone treatment, and that you have to set your clock for looking at a PSA relapse point or undetectable point from the point in time where the patient's testosterone recovered. That, by itself, adds another magnitude of weight.

DR. SCHER: We have designed the study which will enroll patients with doubling times of 6 months or less using the endpoint of an

undetectable PSA at 3 years, accounting for the fact that about 20 percent of the patients will not recover their testosterone levels, and the total duration of hormonal exposure will be 18 months.

So, it is a 3-year endpoint for the trial, and we will hopefully be opening shortly.

DR. HUSSAIN: The last comment is Dr. Eisenberger.

DR. EISENBERGER: Again, I do feel that there are data to suggest that certain PSA changes may, in fact, be a reasonable endpoint at some point in the future.

What we don't have at this point is any correlation between any of these PSA data in a prospective fashion with more conventional endpoints, such as time to progression, for instance. This what we need.

I think what we need is a focus here today, is what does that constitute at this point in time, and not what a 6-month PSA or nadir PSA is following therapy. What are we going to validate that against? That is what you want to know at

this point in time.

DR. HUSSAIN: Just because I said that, ladies go, so that's fine, please.

DR. McSHANE: I think you raise an excellent point and just so that we are not all here again in five years still debating these issues, what can we do now to get the data that we need, so that we won't continue to debate.

I think Dr. Martin from the NCI suggested some very good possibilities. We have several NCI trials. They are ripe for putting in these surrogate endpoints now or these potential surrogate endpoints now, but if we don't decide on what kind of schedule we are going to measure the PSA or at least collect the specimens, so that PSA or something else could be measured, we are going to end up with data that we can't compare across studies and we will still be scratching our heads in five years.

So, I think it would be very beneficial if this committee could--and I know we are running short on time--could spend just a few moments

discussing, you know, if we could have whatever we wanted, what would we do in the way of measuring PSA or collecting specimens, should we collect it on every trial, only in certain kinds of patient groups, should we collect it every 3 months, should we collect it every week, you know, what can se do, so that we are not still debating this issue.

DR. HUSSAIN: Do you want to go a little bit more or you want to wrap it up and this would be the subject of future discussions? Dr. Pazdur, it is 5:05.

DR. PAZDUR: I guess what I would ask is the committee's opinion, would they rather go on with further discussions or wrap things up, because I know we are losing some people because of flights.

DR. HUSSAIN: If I may suggest, I think we have accomplished a fair amount. I do think it's a good idea to have us all digest everything that got said.

If I may wrap up this session dealing with a rising PSA population and the local disease, I

would say the local disease, there is really no consensus or plans at this moment. The rising PSA, what has been put for discussion is perhaps one of two possibilities, as was suggested, begin looking at some validation of certain surrogacy endpoints and the ongoing trials or the planned trials for the rising PSA population.

The other alternative is to bite the bullet and say we have enough data on from retrospective series showing that certain doubling time or some PSA kinetic is likely to predict for poor prognosis patients and begin then targeting those patients for clinical trials. Is that a fair assessment?

Mario, I am going to have to cut the discussion.

I want to thank the Committee members for a wonderful discussion. Before I end, I want to thank especially the public, particularly patients, patient advocates, patients' families, those who are interested and concerned about prostate cancer.

I want to thank you all. Please know that

we are all here because we have patients' interests at heart, no other real issues, and thank you very much.

[Whereupon, at 5:11 p.m., the meeting was adjourned.]

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