FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

Afternoon Session

Wednesday, September 14, 2011

1:00 p.m. to 5:00 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:02 p.m.)

Call to Order

Introduction of Committee

DR. WILSON: I'd like to call the meeting to order. And, once again, why don't we go around the room, starting at the end with Dr. Curt, please state your name and what your background is, and we will go from there.

DR. CURT: I'm Gregory Curt, medical oncologist and industry representative.

DR. MANN: Bhupinder Mann, medical oncology. I'm in the clinical investigation branch at the Cancer Therapy Evaluation Program at the NCI, and I carry GU and adult brain tumor portfolios.

DR. GARNICK: I'm Marc Garnick, medical oncologist at the Beth Israel Deaconess Medical Center in Boston, which is part of Harvard Medical School. I have a predominant interest in GU oncology.

DR. RAGHAVAN: Derek Raghavan. I'm president of the Living Cancer Institute in

Charlotte, North Carolina, professor of medicine at UNC.

DR. EISENBERGER: Mario Eisenberger, medical oncology at Johns Hopkins. I have an interest in prostate cancer.

DR. PENSON: I'm David Penson. I'm a urologic oncologist. I run the Center for Surgical Outcomes and Permanent Surgical Quality and Outcomes Research at Vanderbilt University.

DR. LOGAN: Brent Logan. I'm a biostatistician at the Medical College of Wisconsin.

DR. WOZNIAK: Antoinette Wozniak. I'm a medical oncologist at the Karmanos Cancer Institute in Detroit.

DR. KELLY: William Kelly, medical oncologist, Thomas Jefferson University in Philadelphia.

DR. SEKERES: Mikkael Sekeres, medical oncologist, Cleveland Clinic, in Cleveland, Ohio.

DR. WILSON: Wyndham Wilson, medical oncologist, National Cancer Institute.

DR. BRIGGS: Caleb Briggs, DFO, ODAC.

DR. FREEDMAN: Ralph Freedman, gynecologic oncology, M.D. Anderson.

DR. ARMSTRONG: Deb Armstrong, medical oncologist, Johns Hopkins in Baltimore.

DR. LOEHRER: I'm Pat Loehrer, medical oncologist and director of the I.U. Simon Cancer Center in Indianapolis, Indiana.

DR. ZONES: I'm Jane Zones, and I'm a medical sociologist, and I'm the temporary consumer rep.

MR. ANDERSON: I'm Jim Anderson. I'm a patient rep, 18-year prostate cancer survivor.

DR. JOHNSON: John Johnson, clinical team leader, FDA.

DR. NING: Yang-Min Ning, medical officer for tumor malignancy at FDA.

DR. KLUETZ: I'm Paul Kluetz, a medical officer at the FDA.

DR. JUSTICE: Robert Justice, director, Division of Oncology Products I.

DR. PAZDUR: Richard Pazdur, office

director.

DR. WILSON: Welcome.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's meeting will be a fair and open forum for the discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take are that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the

media until its conclusion.

I would like to remind everyone present to please silence your cell phones and other electronic devices, if you have not already done so. The committee is reminded to please refrain from discussing the meeting topic during the breaks or lunch. Thank you.

I have a conflict of interest statement to be read.

Conflict of Interest Statement

DR. BRIGGS: The Food and Drug Administration, FDA, is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with the federal ethics

and conflict of interest laws, covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act, FD&C Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflicts of interest.

Under Section 17 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of

this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

The agenda for this afternoon's session involves considering the development of products for the treatment of patients with non-metastatic castration-resistant prostate cancer, CRPC, who have a rising serum level of prostate-specific antigen, PSA, despite being on androgen deprivation therapy, ADT.

There are no products currently approved for this indication. No specific products will be presented or discussed. Rather, the committee will be asked to consider possible trial designs and suitable clinical endpoints to establish efficacy that would support a labeled indication for

treatment of non-metastatic CRPC after PSA progression on ADT.

Because ADT is an unproven therapy for this condition with serious long-term toxicity, the committee will be asked whether approval of a new therapy in conjunction with continued ADT would be appropriate for patients with non-metastatic CRPC. This is a particular matters meeting during which general issues will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the issues being discussed today.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Gregory Curt is participating in this meeting as a nonvoting industry representative acting on

behalf of regulated industry. Dr. Curt's role at this meeting is to represent industry in general and not any particular company. Dr. Curt is currently employed by AstraZeneca.

With regards to FDA's guest speakers, the agency has determined that the information to be provided by the speakers is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speakers.

Dr. Scher has acknowledged that he has contracts and/or grants and is a researcher for Ortho Biotech Services, a division of Cougar Biotechnology. He is an uncompensated consultant for AstraZeneca, and is a compensated consultant for Amgen, Ortho Biotech Services, and Millennium. Lastly, he is a scientific advisor for Amgen and Ortho Biotech. As a guest speaker, Dr. Howard Scher will not participate in committee deliberations nor will he vote.

We would like to remind members and temporary voting members that if the discussions

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

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue.

Thank you.

DR. WILSON: Thank you. We will now proceed with the FDA's presentation.

FDA Presentation - Paul Kluetz

DR. KLUETZ: Good afternoon. My name is Paul Kluetz, and I'm a medical officer with the FDA's Office of Hematology and Oncology Products. I'll be giving the introductory FDA remarks for this Oncology Drug Advisory Committee meeting.

As was stated, this afternoon is intended to be a discussion regarding the challenge of developing drugs for the treatment of a specific prostate cancer population, known as non-metastatic

castration-resistant prostate cancer. There will be no formal voting for this ODAC, as it's intended to generate scientific discussion surrounding several issues to this unique population.

In addition to my presentation, we'll hear from two experts in the field of prostate cancer research, following which we'll discuss several discussion points to facilitate the advisory committee discussion.

Listed on this slide are the FDA review team for this ODAC presentation, and I'd like to provide my thanks to each member of the review team for their time and assistance for this presentation.

Here is a general outline of my presentation. I'll begin with a discussion of the background of this population, including a regulatory history, some prostate cancer recurrence information in the PSA era, and, importantly, the early use of androgen deprivation therapy, which has resulted in the population of non-metastatic castration-resistant prostate cancer.

I'll follow this with a discussion of

possible trial design and endpoints in this population, and will finish by introducing some issues for discussion.

So with respect to the regulatory history, there are currently no FDA-approved products indicated for the treatment of men with non-metastatic castration-resistant prostate cancer. However, depending on the trend for early use of androgen deprivation therapy for PSA recurrence, this population is becoming quite large, and we've begun to see an increase in inquiries for development of products to treat non-metastatic patients.

Based on the unique challenges associated with the study of this population, the FDA would like to discuss concerns regarding the non-metastatic castration-resistant prostate cancer population and the design of clinical trials, including endpoint selection, intended to assess the clinical benefit of drugs targeting this population.

So we all know that prostate cancer has

become the most common cancer in U.S. men, with approximately 220,000 cases per year, and that there was a dramatic increase in the incidence of prostate cancer noted in the late '80s to early '90s, with the advent of the serum prostate-specific antigen, or PSA, test. And since the advent of PSA testing, most men are diagnosed with localized asymptomatic disease.

The primary therapy options for these men traditionally have included radical prostatectomy and radiation therapy. However, because of the indolent nature of certain subsets of prostate cancer, active surveillance for certain low risk patients is increasingly being used.

Unfortunately, despite earlier detection and advances in both surgical and radiation techniques, between 15 to 40 percent of patients develop recurrence of disease within 10 years of primary curative treatment.

While a subset of patients with PSA recurrence may be cured with salvage local therapies, the remainder to continue to have rising

PSA, and disease at this point is frequently incurable. The natural history of untreated metastatic prostate cancer patients with rising PSA is widely variable and progression to metastatic disease or cancer-related death can be quite prolonged.

This figure here illustrates the clinical states. And to orient you, the red line is a patient's PSA, and this is the states from local prostate cancer to metastatic recurrent prostate cancer.

So as we've seen, a third of patients after primary local therapy will progress. And because of the sensitivity and wide access to PSA testing, the majority of these patients will progress with PSA only and without any evidence of radiographic or clinical metastases.

These patients can be observed until the development of symptomatic metastases, at which point delayed androgen deprivation therapy can be initiated. Again, PSA reduction will accompany delayed androgen deprivation therapy. However, the

PSA response and palliation of symptoms varies in time, but most patients will eventually become resistant to primary ADT.

Finally, when there is rising PSA or other evidence of disease progression, the final disease state of metastatic castration-resistant prostate cancer is attained. And it's this second disease state of PSA-only recurrent disease that will be the topic for our discussion today.

So as I stated, biochemical recurrence is the second disease state, or PSA rise in the absence of metastases. What's the natural history of this biochemically recurrent cohort? And there's been a number of retrospective series that have looked at this in patients following radical prostatectomy with rising PSA who were untreated until metastases.

Pound described a series of Hopkins patients in 1999, showing that the median time to metastatic disease was eight years. Seventeen percent of this cohort died a median of five years after the time of metastases. In 2005, Freedland updated a series

from Hopkins and noted that with his series, median overall survival had not been reached in 16 years of follow-up.

Now, more recently, Antonarakis presented in 2011 a series that was more diverse from five institutions and also including 30 percent of patients that were non-Caucasian. In his series, the median metastases-free survival was nearly 10 years, and his median overall survival estimate was greater than 23 years.

This simply shows that unselected prostate cancer patients with PSA-only recurrence can have a long natural history and may die of other non-cancer causes.

Given the long times to cancer-related endpoints in unselected populations, there has been an attempt to isolate factors that may predict increased risk of metastases and death for those with PSA recurrence. And based on several retrospective series, short PSA doubling time, high Gleason score, and short time from primary therapy to biochemical recurrence have all been associated

with a higher risk for prostate cancer-specific morbidity and mortality.

Using all three of these predictors, Freedland was able to identify the highest and lowest risk groups in his series, with the high risk group having a five-year prostate cancer-specific survival of 50 percent, while the low risk group had a 15-year prostate cancer-specific survival of 80 percent.

While there are no approved products for men with rising PSA, like those in the Pound series, early use of androgen deprivation therapy with gonadotropin-releasing hormone analogs is frequently used. And it's this early use of ADT in the non-metastatic patients that results in the clinical state known as non-metastatic castration-resistant prostate cancer.

This is illustrated again in this figure, and as you can see from the red line representing PSA levels, when early ADT is employed in the non-metastatic setting rather than waiting until the appearance of symptomatic metastases, the patients

typically have PSA decline, many times below detectable levels.

Unfortunately, while response times vary, the majority of patients experience recurrent sustained increases in PSA despite castrate levels of testosterone; again, creating this new clinical entity, outlined in blue and shaded, of non-metastatic castration-resistant prostate cancer.

Secondary hormonal therapy, such as anti-androgens, ketoconazole or steroids, have been tried in this population, but many of these patients will eventually experience progression of their disease to metastatic castration-resistant prostate cancer.

As we will see, when unselected for high risk patients, even those who have failed hormones, these castration-resistant non-metastatic patients can have a heterogeneous and potentially prolonged course.

There are several FDA-approved GnRH agonists that are used for androgen deprivation therapy to produce medical castration. In the advanced

prostate cancer setting, the two most commonly used in the U.S. are listed here, Goserelin and Leuprolide, and these indications are for the palliative treatment of advanced carcinoma of the prostate. As the non-metastatic PSA-rising population is frequently asymptomatic, early ADT in that population is done off-label.

So are there data to support the use of early ADT in PSA-only recurrence? Well, it's well known that androgen signaling plays a critical role in prostate cancer growth. But while reduction of circulating testosterone to castrate levels, either through orchiectomy or, more frequently, GnRH analogs, have been shown to be active in prostate cancer and may delay clinical metastases in patients with high risk disease, the clinical benefit of ADT in the asymptomatic non-metastatic prostate cancer setting is quite controversial.

Available data have been unable to show a survival benefit from the use of early versus delayed ADT in the asymptomatic non-metastatic setting.

Furthermore, any potential benefit of early ADT, especially asymptomatic non-metastatic recurrent PSA patients, must be weighed against the toxicity associated with the long-term use of androgen deprivation therapy.

Aside from the significant quality of life side effects, including loss of libido, erectile dysfunction, hot flashes, gynecomastia, weight gain, and increased body fat, there are medically serious side effects, including osteoporosis, a risk for fracture, cardiovascular disease, and diabetes.

Earlier use of ADT exposes asymptomatic patients to these toxicities for a considerably longer period of time. And more recent data suggests that longer exposure with higher cumulative doses of GnRH agonists can be associated with higher incidence of non-prostate cancer deaths. And thus, it must be stressed that when considering the risk-benefit ratio for any treatment, a greater weight would naturally be placed on an agent's toxicity when the target

population is asymptomatic and the disease, especially in unselected patients, more indolent.

So what are the clinical practice guidelines followed in the community? Well, the ASCO 2007 guidelines on initial hormonal management of androgen-sensitive metastatic recurrent or progressive prostate cancer note that the panel could not make a strong recommendation for early ADT initiation. And when looking at the current NCCN guidelines, they state the benefit of early ADT is not clear, and treatment should be individualized until definitive studies are completed.

So given this, what drives the early use of androgen deprivation therapy for PSA-only recurrence? Well, there's data primarily supportive of delay of disease progression from more advanced or metastatic populations.

Another important piece is the availability now of reversible medical castration. This isn't new, but it certainly is an easier decision to have reversible medical castration than orchiectomy.

Finally, there's patient anxiety over rising PSA levels, which also has importance in trial design in this population. Anyone who's treated prostate cancer patients can attest to the significant emotional effect a steadily rising PSA will have on a patient, and it's been shown actually in studies that patient anxiety scores and multivariate analysis can predict the use of early androgen deprivation therapy.

So we've seen the natural history of non-metastatic patients that were untreated until metastases, the Pound series, the Freedland, and the Antonarakis series. What's the natural history of those who have failed hormones, the non-metastatic CRPC setting? This is a critical question for the rational trial design in this setting and selection of endpoints. There are a few published studies performed in the non-metastatic CRPC setting which we can briefly review.

Results from the large phase 3 trial of atrasentan and endothelin-A receptor antagonists

versus placebo in 941 non-metastatic CRPC patients was published in 2008. The primary endpoint for this trial was time to progression. And while the trial failed to find a significant difference in its primary endpoint, important data regarding median time to reach primary and secondary endpoints was published, including a median TTP of approximately two years and median overall survival of about four years. Recall retrospective series form the pre-hormone patients having a median time to metastases of eight years.

A randomized trial with zoledronic acid versus placebo, again, in non-metastatic CRPC patients, was halted early for lower than expected event rates. Smith and colleagues published data from the placebo arm of this trial, whose primary endpoint was time to first bone metastases. The results revealed that at two years, 33 percent of patients developed bone metastases and 21 percent of patients had died. The median bone metastases pre-survival was 2.5 years and the median time to bone metastases and overall survival were not

reached. And, thus, even following the failure of hormones, the non-metastatic CRPC population's time to cancer-related events in unselected populations can be prolonged.

Recognizing the limitations of cross-study comparisons and looking at the natural history of non-metastatic CRPC, the time to reach events such as progression and survival can be significantly shorter when compared to the non-metastatic hormone naive patients seen in retrospective series like Pound's. This is partly due to the fact that unselected non-metastatic CRPC patients are relatively enriched compared to hormone naive patients.

Early ADT is typically not initiated immediately upon biochemical recurrence, and some physicians are likely using clinical predictors for high risk disease, such as Gleason score and PSA kinetics, to initiate early ADT in the non-metastatic setting.

However, even following the failure of hormones in non-metastatic CRPC, there is

heterogeneity in outcomes, with the atrasentan trial being able to be completed and the zoledronic acid trial failing to complete the trial due to events.

I think this just highlights, again, that ensuring a trial population, which is enriched for high risk patients, through carefully designed inclusion and exclusion criteria would reduce heterogeneity and allow for more rapid trial completion -- or may allow for more rapid trial completion.

So I'd like to now go on and discuss some trial design and endpoint considerations in this population. Our discussion today is intended to highlight challenges in the non-metastatic CRPC population with respect to designing trials to provide evidence of clinical benefit.

How can we obtain substantial evidence for regulatory decision-making through optimal trial design and endpoint selection?

With this in mind, it's instructive to review the regulatory basis for drug approvals in

the United States. There are two approval pathways in the U.S., regular and accelerated approval.

In regular approval, it's based on substantial evidence of clinical benefit demonstrated prior to approval, based on prolongation of life, a better life, or an established surrogate for either of the two.

Accelerated approval is based on substantial evidence based on a surrogate endpoint that is reasonably likely to predict clinical benefit. This distinction gains relevance as we discuss possible endpoints for trial design in the non-metastatic CRPC setting.

For this discussion, we can consider two possible trial designs for the non-metastatic CRPC population, although many others are possible. Trial design number 1 is the traditional concurrent design comparing the investigational agent to a comparator or placebo. This design was used with a placebo arm in both the atrasentan and zoledronic acid trials, previously discussed.

For drugs that have already been approved in

the metastatic or more advanced setting, another possible design seen is study design number 2, maybe comparing immediate therapy versus delayed therapy.

In trial design number 1, the concurrent comparison design, non-metastatic CRPC patients would be randomized to either investigational drug or a comparator. And while there are multiple primary endpoints for such a design, the most frequent endpoints in published trials and also submitted to the FDA have been related to progression, time to bone metastases, time to metastases or metastases-free survival.

From a regulatory standpoint, these endpoints remain unestablished surrogates for clinical benefit. Patients would then be followed until death, and overall survival has typically been a secondary endpoint.

When moving an agent already approved in the metastatic setting forward to the non-metastatic setting, one may wonder whether you're simply moving the identical response and duration of

response earlier in the disease with no net change in overall clinical outcome. And in this case, one may consider the second trial design and the immediate versus delayed trial design. Patients would be randomized to immediate treatment, seen as drug X or observation. If including a pain endpoint in your progression criteria, you would want to use placebo.

Upon progression, the early treatment arm would be taken off drug X and provided standard of care and followed for survival. On the observation or placebo arm, upon progression, they would be offered drug X, again, followed until predefined progression criteria, at which point they'd be taken off, offered standard of care, and, again, followed for survival.

The primary endpoint of this trial design would need to be overall survival. There is some precedence for this sort of design in prostate cancer and the early use of versus late use of androgen deprivation therapy. The clear difference with androgen deprivation therapy versus most non-

hormonal therapies is that once started, ADT is typically not stopped even after progression.

The merit of trial design number 1 rests in a more clear determination of clinical benefit, with the established endpoint of overall survival. And, also, for drugs that may not be stopped after progression, such as androgen deprivation therapy, this design can determine whether one can avoid some of the long-term toxicity seen with the agent.

There is an understandable concern regarding the feasibility of trials using overall survival as an endpoint if a disease has a variable and potentially prolonged natural history. However, as we've seen, one trial in the unselected non-metastatic CRPC setting revealed a median overall survival of four years, and it may be that non-metastatic CRPC patients selected for high risk disease will result in median overall survivals of less than that.

Regardless of which trial design one chooses, the assessment of clinical benefit relies on careful selection of primary endpoints.

Clinical benefit can be likened to meaningful improvements in how a patient feels, functions or survives. And with respect to patient survival, there have now been four approvals since 2004 in recurrent metastatic prostate cancer and have all used overall survival as their primary endpoint.

How a patient functions or feels has also been looked at with endpoints associated with symptoms and side effects of cancer used for the approval of bone-targeted therapies, using skeletal-related events, as well as mitoxantrone using a composite pain endpoint.

Giving a meaningful magnitude from a regulatory standpoint, these endpoints have been recognized as directly related to clinical benefit. As mentioned, the proposed endpoints we have seen in the literature for non-metastatic CRPC have used radiographic asymptomatic progression. It's important to recognize, again, that asymptomatic progression in prostate cancer remains an unestablished surrogate for clinical benefit. No prostate cancer drug has been approved based on

isolated asymptomatic radiographic profession endpoints to date.

The efficacy assessment for any design using a time to metastases endpoint obviously relies on radiographic scanning, with bone scan and CT or MRI performed periodically every three to four months after randomization. Progression criteria radiographically is by bone scan, usually the occurrence of at least one new lesion confirmed by CT; and by CT or MRI, new lymph nodes greater than 2 centimeters or new appearance of any visceral lesion.

There are concerns regarding radiographic progression endpoints in the absence of symptoms in prostate cancer. With respect to the reliability of measurements, we know that 90 percent of prostate cancer metastasizes to the bone and that bone scans are challenging to interpret. And then there's also the issues of trial conduct, including missing data and possible asymmetric tumor assessments.

Even if one is diligent in the collection of

their radiographic data, the appearance of asymptomatic metastases remains an unestablished surrogate for true clinical benefit. The question remaining, what absolute and relative magnitude of delay in asymptomatic progression endpoints may predict meaningful clinical benefit? In other words, what level of prolongation of time to metastases or metastases-free survival would result in a clinically important delay in cancer-related symptoms or overall survival? And it's this type of uncertainty that's removed when one uses a survival endpoint.

So, in conclusion, I've attempted to introduce the unique prostate cancer population known as the non-metastatic castration-resistant prostate cancer and highlighted several key features. Number one, non-metastatic CRPC is the result of early off-label use of androgen deprivation therapy. Number two, non-metastatic CRP is heterogeneous with respect to natural history, but can be enriched based on known predictors of prostate cancer-related morbidity

and/or mortality.

For products already approved in the metastatic setting, early versus delayed trial designs may be more instructive regarding true clinical benefit. And, finally, with an enriched population, more established endpoints, including overall survival and time to symptomatic progression may be considered.

I'd like to end with a couple of issues for discussion, and we'll, again, revisit these prior to the ODAC discussion.

With respect to patient population, patient selection, we'd like the ODAC to discuss patient selection for non-metastatic either hormone naive or castration-resistant prostate cancer patients for trials intended to demonstrate clinical benefit. And if trials should be limited to high risk patients, to discuss how high risk patient populations should be defined.

With respect to trial design and endpoints, study designs in asymptomatic, non-metastatic, hormone naive, and CRPC patients will be discussed.

We'd like to discuss endpoints to be used for each type of design. And for the trial design number two, the immediate versus delayed design, discuss potential disease progression criteria to initiate delayed treatment.

Finally, with respect to approval pathways, what might be endpoints reasonably likely to predict clinical benefit in non-metastatic PSA recurrent prostate cancer populations and, in relationship to that, the role of accelerated approval with overall survival as the endpoint for confirmation of benefit.

Thank you very much.

DR. WILSON: Okay. I would like to now invite Dr. Nelson to the podium.

Guest Speaker Presentation - Joel Nelson

DR. NELSON: Well, I want to thank the FDA for inviting me to participate in this meeting. I was asked to expand a little bit on some of the things that you've already heard and perhaps paint them in a slightly different point of view from the perspective of a clinician, and, also, one who has

been involved in clinical trials that have specifically targeted men in this disease state.

I think it's important to recognize that we have seen a major change in the presentation of prostate cancer since PSA was widespread in its use. So prior to the PSA era, about a quarter of men presented with metastatic disease, about a third had locally advanced disease, and less than half had what we consider to be curable, clinically localized disease.

It's fundamentally different now. Over 85 percent of patients who come in have clinically localized disease and something less than 2 percent present with metastatic disease.

What does this mean? This means that most patients who present with prostate cancer will be at least offered or there will be discussion about management of their primary tumor, whether that be observation, radiation, surgery.

I'm going to talk about several different tools that we use to assess risk during the talk. And so to set the stage for this, I'm just going to

run through these relatively quickly.

The D'Amico risk categories take advantage of PSA, the Gleason score of the tumor and the T stage, in some various combinations to stratify risk by low, intermediate, and high risk. And these are really quite easy to apply once you learn them. You can immediately tell a patient which risk group they're in. Unfortunately, because they're easy to apply, they're actually somewhat imprecise for particular disease states that may overlap from one group to the other.

One of the earliest tools that we had were the so-called Partin tables, which took advantage of a large database of men who underwent radical prostatectomy, and using the PSA stage in biopsy, Gleason tried to predict what the final pathologic outcome of those patients would be. And this gives the patient a snapshot of their disease state. But, unfortunately, these have required updating regularly because the type of disease we see presenting going on to surgery has changed in the sense that it's generally not as bad as it once

was. And so the pertinence in 2011 is questionable.

The group in UCSF expanded on the Partin table by adding the age of the patient and the degree of positive course, coming up with a somewhat more stratified 1 through 10 score, which I personally find to be rather cumbersome and difficult to handle.

I think the current state-of-the-art in this area are nomagrams. The champion and author of these has been Mike Kattan and the group at Memorial Sloan-Kettering, which take continuous and categorical inputs. These are highly individualized. But, unfortunately, you really need to use a computer, and most of us will use these in the clinical setting regularly with our patients.

So what has been the change? And I'm sorry for the title. This should be the change in risk categories of prostate cancer at initial presentation. Well, in the early '90s, it was about a third, a third, and a third, low,

intermediate, and high risk. And currently, now, about half of the patients who present have what we would consider to be low risk features, and only a fraction of these patients have high risk disease.

Taking advantage of a national database known as Capture, Matt Cooperberg has looked at, based on your CAPRA score -- CAPRA scores 0, 1 and 2 would be considered low risk, 8, 9 and 10 would be high risk, and everything in between would be intermediate risk. You can see that the application of various management corresponds actually quite well with the disease state, with radical prostatectomy being used primarily in patients who had lower CAPRA scores, and primary androgen deprivation therapy in those who have higher risk scores. And this is community-based and also some academic-based practices.

It's also interesting to see that based on the particular clinical site of care, there's tremendous variability on how these therapies are applied. So there is clearly not consensus on what would be the best therapy at any particular

clinical site. And if you look across the bottom here, you can see increasing risk scores at various sites, and, yet, there's really no consistency on decisions about what patients are offered. It's often based on the clinician themselves, a theme that I will be coming back to.

Well, if I look at my own personal series of men who have undergone radical prostatectomies by me since 2000, the majority of these patients actually have curable disease with surgery. And so roughly 70 percent of these patients have no evidence of disease recurrence at five years.

I think it's important to emphasize that prostate cancer is not all the same. And I know that this may seem to be a simple-minded proposition, but when we look at things where we say there's an eight-year time to metastases, you have to understand what's giving you that figure is the diversity of the disease.

Salvage radiotherapy applied to recurrent prostate cancer after radical prostatectomy was studied by Andy Stephenson in a multi-institutional

cohort of patients, and you can see that these patients actually do not really respond very well over this period of time, with less than half of them at five years still free of disease.

The sad part about this is that the patients that you would want to benefit the most from having salvage radiotherapy, those with high risk features, those who have rapid PSA doubling times, actually are most likely to predict failure from this salvage radiotherapy.

Andy Stephenson has also looked at a large group of men who have undergone radical prostatectomy and asked the question, now that we have long-term follow-up, what is the prostate cancer-specific mortality? And you can see that over 15 years, you have about a three times higher chance of dying of a non-prostate cancer death if you were eligible and underwent a radical prostatectomy than specifically dying of your disease.

If you look at the variables that would perhaps predict for a specific prostate cancer-

specific mortality, obviously, high Gleason score, poorly differentiated tumors populate this group. And about a third of the deaths that occurred had Gleason 8 to 10 disease, but only a fraction of the total cohort of patients actually had Gleason 8 to 10 disease, 6 percent.

Likewise, locally advanced tumors had a higher prostate cancer-specific mortality, but only 2 percent of patients who were offered surgery had T3 disease, high PSA, likewise. And if you use the D'Amico high risk group, which is somewhat broader in its definition, the 15-year prostate cancer-specific mortality of so-called high risk disease is under 20 percent in this cohort. It raises the question, how can you define something as high risk when 80 percent of the people don't actually die of the disease if you apply surgery to them.

So it's important to recognize that adverse clinical features overall in prostate cancer are relatively rare, and most patients who were treated with surgery, in fact, do not die of prostate cancer.

Scott Eggener has taken these data and developed a nomagram, a snapshot that you could apply to a patient immediately after surgery based on other clinical features. And you can see the length of the line here determines how much it contributes to the strength of the observation. So primary Gleason score, secondary Gleason score, and local invasion into the seminal vesicle are the largest contributors to the possibility of dying of prostate cancer after surgery.

Anthony D'Amico was one of the first to recognize that if you looked at the PSA kinetics after definitive local therapy, whether it be surgery or radiation, and you looked at that cohort of patients who had a PSA doubling time more rapidly than every three months, you can see that prostate cancer-specific survival for that group was not good. And if you compare them to the group that have overall survival, you can see that these curves are essentially superimposable, which would indicate that almost all the deaths that occurred because of prostate cancer in men who had rapidly

rising PSAs, less than three months.

Steve Freedland has looked at this in the Hopkins cohort of patients who underwent radical prostatectomy, and that analysis had no incident where there was a patient who had a PSA doubling time less than three months who died of a non-prostate cancer death. So PSA kinetics actually predict very well for the possibility that you'll die of prostate cancer.

One of the criticisms of this study has been that, in general, the Hopkins cohort is younger and healthier. And so the risk of them having a competing cause of mortality is lower than what you would expect in the general population.

Looking at this from a different perspective, the Hopkins group also looked at metastasis-free survival and untreated biochemical recurrence after prostate cancer. And you can see that if you take all comers, it's about 10 years. But I think it's important to recognize that this is a very diverse group.

So if we break these out by Gleason score,

you can see that those who have high grade disease have about a four-year median time to metastasis, and these are in men who have untreated, never saw hormone therapy prior to developing biochemical -- developing metastases.

Likewise, the PSA kinetics that one applies to these patients is very predictive of the likelihood they would develop metastatic disease. So if a patient has a PSA doubling time of less than three months in this group, at one year, they would have metastatic disease.

One of the points the previous speaker made was the issue of palliation for advanced prostate cancer. And as a clinician, I will tell you that a man who has a PSA doubling time more rapidly than three months is extremely anxious, as am I. And so you could say, well, maybe you're not physically palliating that patient, but by applying androgen deprivation, you change at least the kinetics of this phenomenon, at least in the short term, and there's a clear psychological palliation that occurs.

Then, finally, looking at metastasis development from the Memorial group, you can see that both trigger PSA, PSA slope and PSA velocity were the largest contributors to trying to determine who would develop a positive bone scan in patients who had not yet seen androgen deprivation after radical prostatectomy.

Switching gears here. The heterogeneous use of androgen deprivation for prostate cancer is one of the things that we see in our field. And, unfortunately, there is inappropriate use of these agents. In the primary use for low grade, localized disease, there is no evidence of efficacy in clinical trials. In fact, there is some evidence that if you applied such therapies to patients, they may have an excessive death from other causes associated with androgen deprivation use.

But there clearly are appropriate uses for androgen deprivation. In combination with radiation therapy in locally advanced or high grade disease has been shown repeatedly in clinical

trials, randomized clinical trials, to have an improved overall survival. No positive disease has been shown. In a smaller trial to show overall survival benefit, if the patient also underwent a radical prostatectomy, clearly, patients who have distant metastases will benefit from this.

I would argue -- I put a question mark here because I can't point to a trial. But if you have high risk biochemical recurrence after definitive local therapy, such as defined by a short PSA doubling time, that would be an appropriate place to apply androgen deprivation.

Our field, though, has been -- and now I'm speaking specifically as a urologist. Our field, unfortunately, has shown themselves not to be judicious in their use of androgen deprivation.

So this is a study that looked at about 800 urologists around the country at what would be considered uncertain benefit use of androgen deprivation. And you can see that, overall, about 35 percent of the use across the entire population was defined by what would be considered an

inappropriate or uncertain benefit use. And the dark bars at the bottom are urologists that never did this, and the bars at the far left-hand side regularly applied androgen deprivation in this setting.

These investigators have gone on to try to understand the nature of the urologists that applied this, and, not surprisingly, I would say that those who have no academic affiliation in the community and private practice seem to use androgen deprivation in an uncertain benefit setting more often than those who are affiliated with an academic medical center.

Interestingly, when CMS changed the way that androgen deprivation was reimbursed in this country, dropping it by over 50 percent, I think it's important to recognize that about 40 percent of the revenues made by community urologists in private practice prior to this change were accounted for by the use of androgen deprivation. But going along with this decline in the reimbursement, there have been actually two

declines by CMS, we are now seeing that inappropriate use of androgen deprivation has actually declined on a national level.

Then I'd leave you with this about androgen deprivation. These are data collected from a 5 percent Medicare cohort, 1992 to 1994, and then followed. And you can see that if you were in Medicare, so 66 years and older, and followed, that the median all cause survival was only 52 months, and less than 10 percent of patients to whom androgen deprivation was applied were still alive at seven years. I think it should give us all pause about the widespread use of this therapy, and we should, I think, arguably, use it in a more targeted fashion.

Well, what are some of the challenges in trial design and what we would call M0 or rising PSA in the non-metastatic patient? Well, Matt Smith studied this or was involved in a study of zoledronic acid that was closed and he was able to demonstrate for us this long natural history.

So 201 patients with non-metastatic disease

and rising PSA despite androgen deprivation, at two years, only about a third of them had developed bone metastases, and the median time to the first bone metastasis had not been reached by 30 months. And these are the curves that came from that publication. You can see that when you get out to about three years, death and bone metastases begin to compete. And the event rate was so low that the sponsor of the study closed it.

But what Matt was able to tell us was that if you actually looked at the PSA of the patients or their kinetics, and their kinetics, you can separate the patients who would have rapid progression from those who you would expect not to have rapid progression to bone metastases.

Matt and I have taken the atrasentan study, the placebo arm of the atrasentan study that was in this space, and showed that at 25 months, it was the median time to bone metastases, and that time to death in this group was almost four years. And supporting his earlier observation, if we looked at quartiles of PSA levels, you can see, again, that

PSA is pretty predictive of disease progression to development of metastases in men who have castration-resistant prostate cancer.

Maha Hussain has looked at men who have metastatic prostate cancer, but I think the same observation we see as clinicians all the time in men who don't have metastatic prostate cancer, which is that if you apply androgen deprivation therapy and you do not see a PSA response that nadir is less than .2, and, indeed, if you still have a PSA, in this case, over 4, that that was very predictive of overall survival.

This was a study where men were randomized to receive seven months of androgen deprivation and then divided to continue androgen deprivation versus having it in an intermittent format. And this is an ongoing study.

She also showed in that same cohort that if you developed PSA progression after the application of androgen deprivation, that that also was very predictive of overall survival. Obviously, there are going to be challenges if you apply a therapy

to these patients who have really very rapidly progressive disease.

I'm going to return to a slide I showed earlier. One of the challenges I think we have in detecting bone metastasis is shown by a blowup of the curve from the atrasentan study. You can see that the assessments occurring every three months really pull out those who are developing bone metastases, but I don't think any of us actually believe that these were not bone metastases that were, in fact, present. It was just the ability for our imaging technique to detect their location before we could call them a metastatic lesion.

So this is the standard planar bone scan using technetium, and, in this case, you can see this patient who has a metastasis in the shoulder, as well as one in the rib. If you apply multifocal spect to this -- and if I was clever, I'd know how to turn that, but I don't -- it actually allows you to detect more bone metastases. But now with an agent that actually was quite old and now has been rediscovered because of the introduction of PET

imaging, sodium fluoride, you can see that you can pick up many, many more bone metastases by using this new agent. And at our center, this is now quickly becoming one of the preferred methods that we use to screen for bone metastases.

It's interesting to note that the background soft tissue in the planar bone scan is significantly greater than the sodium fluoride, which was more avid for bone.

Let me give you one more example. This was a patient with newly diagnosed prostate cancer for whom the planar bone scan was viewed as negative, but then underwent a spect scanning, a CT scan, and then using the fusion of PET CT with fluoride imaging, there's clearly metastatic disease in the thoracic spine. So it may be as we contemplate the trial designs that look at imaging as an endpoint, that, in fact, we try to do a better job at imaging the disease.

I want to bring up one other issue related to trial design in this setting, and, again, this is the study that we've alluded to on several

occasions, atrasentan, to try to delay disease progression and M0 disease. This was a placebo-controlled study, with the onset of metastases being the defined endpoint, and this enrolled 941 men with non-metastatic prostate cancer.

This is the result. There was about a three-month difference between atrasentan and placebo, which was not significant in this study. But if you just look at these curves, you have to ask yourself how could that possibly be. They separate, they stay apart at the median, and then they come back together. But it would look like this should have been a positive trial.

Well, it's very interesting. If you look at where the trial was conducted, the results were very different. So in the United States, men who were randomized to atrasantan appeared to do worse than placebo, whereas men in Canada and Europe, non-U.S. sites, had about a six-month difference favoring atrasentan in this population.

Well, why would that be? I think it's because there was a very large difference in the

cumulative discontinuations by region. So in the United States, atrasentan randomized patients -- this was a double blind study -- dropped out at very high rates, and certainly much higher than we saw in the non-U.S. sites.

Why would that be? Well, if you went back and looked at the PSA change in patients who discontinued in the United States, patients, and perhaps, also, their physicians, in a placebo-controlled study had low tolerance for rising PSA. And the delta PSA from one visit to the next was significantly less than a much higher tolerance for a rising PSA or a delta PSA in non-U.S. sites.

So as we think about trial design, you have to recognize that when you put patients into a placebo-controlled trial who are watching their PSA, which they've been thinking about now for, in some cases, decades, it's hard to have them have fidelity for the trial, and I think that's something you need to wrestle with.

Then I leave you with this. This is work

from June Chan, who looked at the patient population of men who had prostate cancer in 2005, and, as you know, death from prostate cancer is really an age-related phenomenon, with older men dying at higher rates than younger men. Median age in the U.S. right now is about 80.

Well, this event took place in 1945, and as a result, that activity was taken off the streets of Broadway and into the bedroom and the baby-boomers occurred. So I was born in 1960, ostensibly, the last year of the baby-boom. We got older. And now the classic population curve that one sees that's triangular has now become rectangular in our population; that, coupled with the fact that death from heart disease is really dropping considerably in this country. So these are data from the American Cancer Society showing that if you're younger than 85 years of age, your chance of dying of cancer exceeds the chance of dying of heart disease in this country.

So June took these data and just extrapolated them into the future. So in 2025, the

death rate from prostate cancer is expected to increase significantly. And at 2045, when I hope to be 85 years old, the death rate of prostate cancer in men 85 years and older will be greater than all of the deaths that we see currently.

So we face a growing problem, castration-resistant prostate cancer, for which, I argue, you are all going to be challenged.

So what are my conclusions? The clinical features of primary prostate cancer will be predictive of biochemical recurrence, and the PSA kinetics at recurrence will predict metastasis and death, and I think it does it actually, unfortunately, well.

The use of androgen deprivation is often not evidence-based. The progression of non-metastatic castration-resistant is very diverse, and this challenges both trial design and the patients that we would like to enroll into those trials. And, as I said, this is going to be an increasing clinical problem.

So I thank you for your attention.

DR. WILSON: I would like to now invite Dr. Scher.

Guest Speaker Presentation - Howard I. Scher

DR. SCHER: Thank you very much for the opportunity to share some thoughts on the management in clinical trial design issues related to prostate cancer, and, in particular, the state of the disease that we're seeing more frequently; namely, the non-metastatic rising PSA castrate state.

So I'd like to present, first, a framework and following some of the questions raised, discuss the patient population, trial design issues, and, of course, outcomes.

So we know that the disease can be classified as a series of states, which really represent, for the continuum, from the time of first diagnosis to metastatic disease and ultimately death from disease, and immediately we see they're looking at the relationship between diagnosis to death. We know that there are a large proportion of men who have indolent disease who do

not need immediate treatment, and that occurs at all points in the disease continuum.

We know that androgen depletion is the standard, but as we've heard from previous speakers, when to actually administer it remains controversial.

We'll be focusing today on the rising PSA non-metastatic castration-resistant state. But thinking back to and looking back to some of the issues we faced in the early 2000s with the rising PSA non-castrate state, many of these issues, in fact, apply.

This was originally published in the Journal of Clinical Oncology, and this was a group of investigators who had a particular interest in developing trials in this area and are actually working hypothesis at the time, since we're uncertain as to the significance of PSA.

We didn't completely understand the prognosis of the patients, which was a largely heterogeneous group. We knew that in advanced disease, PSA changes can, in fact, be misleading,

when, in fact, a patient can be benefitting from a treatment when it's going up and not necessarily when it's going down.

We knew that there were issues related to patients waiting until the clinical endpoint is achieved in order to remain on study when they're tracking PSAs very closely. And we came out with a formal recommendation not to begin drug development in this group unless more was known about the drug in late stage disease. Our working hypothesis at the time was actually that trials should not be conducted in that population for those reasons.

Since then, we have focused on how do we understand the clinical significance of a rising PSA in the non-castrate state. We try to develop outcome measures that would be meaningful and quantitative and reproducible and bring some standardization to trial designs, and be in the position to actually demonstrate that a treatment offered to a patient, in fact, altered their natural history in a favorable way, with an acceptable safety profile.

So thinking back to the way we conduct all of our clinical trials, we first start with the therapeutic goals. And a point of fact, this is analogous to exactly what we do in practice. We think why are we offering treatment to this particular patient at this particular time; what is it expected to do; and, what is the potential adverse events that might be encountered.

We have a patient population to which we define entry criteria, but now we have to think more closely about the drugs that we're evaluating, because we are moving way beyond traditional hormones and cytotoxic drugs. And we've seen clear evidence that drugs not known to modulate PSA, namely, those affecting the immune system or the bone microenvironment, can, in fact, alter the natural history in a favorable way and prolong life without affecting many of the traditional measures that we're using to assess disease.

We tried to standardize endpoints and have investigators think about their trials in terms of if you achieve your desired outcome, what will you

do next, thinking more along the path to a regulatory approval.

So turning, first, to the patient population. Unfortunately, there does remain some confusion amongst investigators and physicians as to exactly what this state is. And as shown earlier, in fact, it is the patient who receives hormones at a time where they did not have detectable metastatic disease and never show detectable metastatic disease on an imaging study, which contrasts with the patient who has detectable disease, now has a rising PSA and normalization of their imaging studies on scan. And as mentioned earlier, there is no FDA-approved drug for this particular disease.

But looking through clinicaltrials.gov in terms of some of the eligibility requirements and the workups that are being used, you can see that they're quite heterogeneous. In the old days, we were limited to plain radiographs. Most trials include a bone scan, but these are technetium. They have not incorporated fluoride-18.

Computerized tomography is used variably. There are virtually very few trials that are actually looking at bone marrow MRIs, which are quite sensitive in detecting scans. And there are a number of more experimental imaging modalities which are being explored, namely, antibody scans, looking for circulating tumor cells, the clinical significance of which, in that state, is not defined. And there's a large literature that, in fact, if one looks hard enough at the bone marrow, one can, in fact, find cells, some of which may, in fact, be dormant. The clinical significance of this is uncertain at this time. But is this a bone metastasis or not?

But, clearly, when we look at the imaging studies, it is very clear that the interpretations are often very subjective, and, in fact, the way the interpretations are recorded is not amenable to quantitation nor putting into a database. So we, as part of our consortium, have a very large effort to try to qualify imaging biomarkers so that we can address the question of whether or not there are

progression biomarkers that can be shown to associate more strongly with survival, placing us in a position to accelerate -- have the opportunity to apply for accelerated approval of drugs. But the associations of the changes in imaging and clinical outcomes, unfortunately, is sorely lacking.

So looking through the briefing document, does this group of patients represent an unmet need? Yes. It's challenging, but in point of fact, it is a large population who have needs that need to be addressed. It's very difficult to understand the true frequency of this state. When we poll our colleagues, some say it's 3 percent of their populations, others, 20 percent. But this, in part, will depend on how hard you look.

We do know that as the result of prospective trials, we now have a better sense of how to identify risk, which enables us to, in risk, for the patient populations. And one must include in the discussion with this patient group, despite the rising PSA, that in many cases, an important

treatment option for some is not to do anything.

So if we think about how are we understanding prognosis of an individual, again, just to illustrate this more graphically, what happened in the past will impact on what happens in the future. So when one looks at the vertical yellow line, where it's just the time a patient is presenting for a treatment, one has to look back at his original tumor, his prior treatment, his response to the prior treatment, and his current disease status in order to better define the risk of events in that individual going forward. And depending on the probability of risk, one can make a decision whether or not to offer treatment. Too many of the eligibility criteria really do not factor in the prior treatment characteristics and disease course in the individual.

You've seen these slides before, but, again, this does show us that in the context of prospective trials, we now have the ability to better define patient risk and how that is defined going forward. Again, what has been very

encouraging is these criteria appeared to be reproducible within several trials and fairly consistent in terms of the events that have been observed. One could look at the baseline PSA or doubling time and, again, set the bar however everyone wants to do so in the prospective design of the trial.

Again, this has now gone further not only to look at bone metastasis, but bone metastasis or death or death from disease. And, again, these types of factors, I believe, will become the eligibility criteria that will enable us to enrich a population that need treatment because of significant risk of symptoms or death or metastasis from their illness.

But, clearly, the interest in this state has also not -- has increased significantly, because in point of fact, in the past 18 months, there were four agents that were shown to prolong life. And, again, three of them are now FDA approved, but noteworthy is that these are a range of treatments. It's not a traditional cytotoxic. It includes a

biologic. It includes an exclusively bone targeting agent. It includes a hormonal type therapy.

So with the hypothesis that earlier use of a treatment that's more effective in an advanced disease setting will be more effective if used earlier in a minimal tumor setting, the first question that was asked was whether approval of a product would encourage the use of unproven and off-label ADT. I think this is a very important question, but independent of the question that we are, in fact, addressing here, which is addressing trials and how to show benefit in the non-castrate metastatic patient. At least in our own practices at Sloane-Kettering, I do not see this as a motivation in order to start hormonal treatment.

If one thinks of what are the tradeoffs and, as highlighted in course number 1, early treatment given in the rising PSA state may delay the development or frequency of metastatic disease. But, clearly, the longer exposure will increase the risk for treatment-related adverse events.

In scenario 2, waiting until there are symptomatic established bone metastasis may increase the risk of skeletal morbidity, but it would reduce the risk of the ADT-related complications; again, obviously, a very important issue, but I think it's a little bit beyond the scope of what we're addressing here.

So the question is, would it be appropriate to conduct trials in patients with a rising PSA after definitive primary treatment? This is opinion, but I think that it can be done. It's a different type of design. And as you heard from Dr. Nelson, there have been studies now which clearly identify those patients who receive androgen deprivation therapy, ideally, appropriately, in whom a risk for metastasis and death can be identified.

We heard earlier about the Pound experience, where you can see patients who first recur after surgery and who are not treated until symptoms developed. The course can span 14 years or more, as seen by several groups. But one can start to

subset this population looking at a simple factor, such as PSA doubling time and, not surprisingly, more rapid doubling times will associate with significant clinical events, namely, risk of death and prostate cancer-specific mortality.

The challenge is to use these criteria within trials. Unfortunately, in many cases, there is an overzealousness in trying to enroll a trial and the eligibility criteria may, in fact, be broad. We've restricted our trials to patients who have rapid doubling times, but this represents only about 20 percent of the population who recur. But I would argue that it's more appropriate to treat the patients who need them, who are at risk for the events, so that the questions can, in fact, be answered.

As mentioned earlier, it's now clear that those patients who demonstrate clear insensitivity to hormones by not completely achieving an undetectable PSA or, in this study, a PSA of less than 0.2, again, representing about one-fifth of the population, also identifies as group who have a

castration-resistant metastatic disease, at risk for significant prostate cancer mortality.

So given the indolent course in some patients, should trials be enriched for those at risk for prostate cancer-specific mortality? Yes. The treatment effects would be the same in these cohorts, but, obviously, the benefit would be seen more rapidly in an enriched cohort, who, arguably, need it more appropriately. And, clearly, if there were adverse effects, depending on the treatment, clearly, the higher risk of mortality, the more that risk might be acceptable to patients. So the answer, I would say, is yes.

How would you define risk? That will depend on the trial context or clinical practice. We've heard about PSA anxiety. It is not a trivial factor. There are many men who, unfortunately, become dysfunctional when they're focused on their PSAs. But, clearly, what the field needs to do is develop more informative prognostic models so that we can better understand the risk-reward ratio. And I think one of the encouraging outcomes of our

initiative in the early 2000s is, in fact, there are many investigators who collaborated to begin to develop the types of nomagrams that allow us to better ferret out those patients who need interventions from those who do not.

While this is just an opinion, I think if somebody has a risk of bone metastasis of 30 to 40 percent in a two-year period, that would seem reasonable to enroll in a trial. But, again, this will vary by individual and it is certainly not meant to be hard and fast.

So when we start thinking about trial design, we think analogous to what we do in practice. Why are we considering treatment for this patient? Why is the treatment being offered? What are the goals of treatment? We look at the patient's prior history. We look at their current disease manifestations. And in this population, we essentially are left with the PSA.

So a key issue is how do we determine a treatment worked and at what cost. If we look at the approved drugs in castration-resistant

metastatic disease, this supports a paradigm thinking less about a partial remission, but thinking about what the treatment is actually designed to accomplish.

So there are approvals for the control, relief or elimination of pain specifically with radiopharmaceuticals, mitoxantrone and prednisone. We would look at these as early, quote, "response measures." But more importantly or equally of separate import are the time to event measures, which we would say delay or prevent either symptoms or death for disease. There is a formal indication and approval to delay/prevent skeletal-related events with bone targeting agents. And if we think in terms of survival, this can be thought of in terms of delaying or preventing death from disease, and there are four approvals within this category, as well.

There are no approvals, appropriately, based on PSA changes. And because we have not clearly established the significance of various degrees of tumor regression, there are no approvals based on

tumor regressions, per se. But, clearly, we know that survival is one, but it is not the only measure of a clinical benefit.

So for this reason, we think that one should think about each of the potential outcomes as an independent measure. We are not clear as yet about the clinical significance of a solitary bone scan finding, when it might cause symptoms. We know, as we've seen in trials, that a bone targeting agent that results in a higher frequency of extraosseous progression is not a surprise. It should be accounted for in the design.

But we also have the opportunity now to test agents that will affect tumor in any site, both bone and soft tissue, and the designs for each of these will be different. But, clearly, what we need to do is to better understand the natural history of prostate cancer in bone to see what is the probability of skeletal-related events, or significant morbidity, or death from disease in order to be in a position to clearly show a benefit.

So as mentioned, as we understand more of the metastatic process, we're moving beyond simply cytotoxic drugs and hormonal agents. We're seeing that targeting the metastatic process, targeting the bone micro environment, targeting immune surveillance mechanisms, can be therapeutically beneficial and prolong life, and the effects of these drugs cannot be assessed reliably based on the current measures that we are, in fact, using. And there are many other components to the cancer process that are now the focus of major drug development efforts.

One could think about, in terms of PSA changes, I think we've seen a remarkable evolution in thinking about how patients approach their PSA, and we found that if we explain to patients that even if they're getting a cytotoxic drug, it might take three to four cycles before it declines, or there may be a significant delay before you see an effect, or there may be no effect.

Again, if a patient is instructed as to what the anticipated outcome is and what the therapy is

defined to do, we found compliance to be quite good.

So thinking about design number 1; a head-to-head comparison of a drug that has proven efficacy in metastatic disease, now being tested in the non-metastatic castrate-resistant population, focusing on delay to prevent outcome, since we are only relying on PSA.

Most in the trials of these spaces has been quite large, generally over a thousand patients. We're looking at patients where the eligibility would include a predefined risk, focusing, as well, on present status, but prior treatment history and clinical course.

The comparison would be the approved therapy versus placebo, since there is no defined active comparator, and we would be focusing on metastasis-free survival, which does include not only metastasis, or perhaps skeletal-related event survival, which has, again, an established regulatory endpoint.

Secondary endpoints, one could look at time

to bone metastasis, skeletal events, time to a new treatment, which will become an increasing issue, particularly now that there are multiple drugs approved; development of symptoms using validated scales, and, obviously, survival has to be considered and is a very important measure.

But in the design of these trials, there will need to be a change in culture. Again, looking across trials in clinicaltrials.gov, there's a wide range of assessment intervals. They are generally not consistent between trials. All include PSA, which they don't act on.

The use of bone markers is highly variable. The use of bone scanning and timing is highly variable. The interpretation of the bone scan may involve adjudication, but it's not clear that the third person voting is necessarily the right one. Computerized tomography is often used for confirmation. Few trials are using MRI in order to look at disease globally. And, again, as I mentioned earlier, there are a number of other modalities that are being tested.

But, clearly, what is imperative is that we are tracking these patients not only while they are on study, but making sure that when the patients come off study, scans are completed, and then continue in order to understand further progression.

So as we have recommended for the metastatic disease setting, we would focus on individual parameters. Bone progression can involve either new lesions or perhaps growth of existing lesions. SRE is an approvable endpoint. Soft tissue disease, I would be hard-pressed to stop therapy, alleviating pain because a lymph node has now reached 2 centimeters in size, if the patient is feeling better. Obviously, the significance of new visceral disease is much worse than perhaps a slight enlargement in a lymph node.

Bone tumor markers are generally recorded, but I have not seen them utilized consistently in terms of decision-making. And symptoms, obviously, have to be separated as to whether they are related to the disease or a treatment.

So there are a lot questions now. We traditionally continue hormonal therapy. The question is, when should we stop some of the drugs that a patient has been on for a period of time. And we need to understand what is the significance of occurrence of a single event. Is a new lesion important if it's confirmed? Is it more important if it's caused pain when you could perhaps radiate?

The question is, how do we understand when the treatment may not benefitting a patient, and is there a way to actually look at the totality of morbidity if we follow a patient over time, because, in fact, this happens in superficial bladder cancer, the patient may recur and still potentially be benefitting, because, in fact, the frequency of the events has dropped.

Do we necessarily have to stop therapy? Should we add another drug, which is a major issue, because there are now four drugs which have been shown to confer a survival benefit? And, again, since bone metastasis are so significant, would it be a clinically relevant outcome to get a sense of

total bone morbidity over time as a clinical benefit measure?

So we know that if we leave a patient with prostate cancer that is in the non-metastatic castration-resistant state, there are essentially several outcomes that can occur. It will progress. Some may only progress to lymph nodes, others to viscera. But the most common site is to bone, which will ultimately cause pain, epidural disease, may cause fractures or marrow failure, which, arguably, are some of the most feared complications that patients experience with this illness. And I would argue that delaying or preventing that from occurring is a clinical benefit to patients.

The question is, when do we intervene. Do we intervene at the point of pre, before the metastasis are manifest clinically, even though they are likely microscopic? Do we wait until they're established and asymptomatic, or do we wait until they, in fact, become symptomatic?

If we're going to look at time to events, as I mentioned earlier, often, the disease assessments

are stopped after a patient comes off treatment. But given that the significance of many of the endpoints we're looking at is uncertain, it's essentially that we track patients further.

We do have therapies that prolong life. So, again, we'll have to pay closer attention to what happens to the patient subsequently and how that patient responds. And as I mentioned, this is particularly important, because there are therapeutic options which are approved which do prolong life.

So looking at the endpoints, we can look at time to first metastasis; metastasis-free survival, which includes death from disease. SRE is an established endpoint. But the question remains, will it be difficult to continue treatment in the setting of new metastasis or new symptoms short of an SRE? And, in fact, if the treatment is stopped, we may give a subsequent therapy, which could modulate that endpoint and potentially miss an active drug. We feel survival, obviously, is extremely important, but it's not the only measure

of clinical benefit to these patients.

So one of the propositions is something we're exploring with our metastatic patients, which is to require confirmation of new lesions on a subsequent scan as an indication to potentially stop treatment. This is totally a proposal. But, clearly, progression would require the documentation of additional new lesions on a scan, and there are, importantly, a number of new methods that can quantitate both bone -- total bone metastasis burden, as well as tracking new lesions. And these are under development, and they're much more reproducible than some of the interpretations.

Regarding the risk-benefit ratio, if you look at the CONSORT diagrams for a number of the reported trials, tracking carefully is why did patients withdraw consent. I would argue some of these are for the rise in PSA. Non-prone progression for a bone targeting agent, again, reasonable.

Adverse events, these are hypothetical data. When you start seeing a high frequency of adverse

events, one has to question the net benefit of that treatment, particularly if it's modest.

So in trial design number 2, the question was raised whether early versus delayed therapy using a product already approved; then to discuss potential triggers. I'm looking forward to the panel discussion. Personally, I found this a very difficult question, what is the appropriate trigger, again, knowing that there are appropriate -- there are effective treatments.

So if one breaks this down schematically, again, starting treatment, randomizing a patient who is in the non-metastatic rising PSA castration-resistant state, placebo versus the active treatment, one could potentially trigger treatment as soon as a new lesion is seen at point number 1, or one could wait until the patient is symptomatic.

Then for the active treatment, is the first development of a metastatic lesion considered a treatment failure or do you wait? Again, these are potential issues that will have to be considered.

So the question is, when do you add

treatment, a new treatment to the placebo patients, and when do you stop treatment in the active therapy group? All of these will be design considerations.

Again, as I mentioned with the red Xs, two potential points where one might design a stop of treatment, and, obviously, these will have different implications downstream.

We would argue that the trigger should not be PSA-based. Again, requiring some confirmation of a second scan to get a sense of progression I think is something that might be considered. Obviously, extraosseous spread would be anticipated for a bone targeting agent. I believe no one would argue with a clear SRE. This is already an established regulatory endpoint.

But the reality that we face is it will be very difficult to not treat someone once they have clear indications that their disease is worsening radiographically or if they start to develop symptoms. And it's going to also be very difficult to dictate the choice of one treatment, one versus

another, particularly when they have all been shown to prolong survival.

So I want to throw out one point of discussion which was not discussed. And the question is, since we are dealing with a very minimal disease setting, is there a potential, an opportunity for cure and could this be a potential trial design?

So if one thinks about an undetectable PSA, recognizing its limitations, zero versus non-zero is relatively clean. We know that would require a prolonged period of observation, and, ideally, stopping all treatment, including hormones, allowing for testosterone recovery. So if a PSA is zero for a defined period of time and the testosterones are normal, this could potentially be a dichotomist outcome. There would be no equivocation, no debate as to whether it is or isn't. It's binary value.

Again, considering some of the aversive treatments that we're seeing now, the opportunity to stop a treatment that may cause long-term

morbidity is another potential area, and I would just throw that out for discussion.

This would essentially be, again, a head-to-head comparison, and a proposed primary endpoint might be an undetectable PSA. Obviously, there would have to be testosterone recovery and not all patients will do that after a period of time, time point to be negotiated. Obviously, one could also look in the short-term how many patients achieve that endpoint and a time to PSA failure simply as a screen.

So the agency's position, again, is that drug development in the non-metastatic PSA recurrence population should focus on high risk. We agree completely. The preferred endpoint of clinical benefit in prostate cancer is prostate cancer-specific survival.

We would agree that this is an important endpoint, but, again, this will become more difficult, I think, to achieve with the confounding therapies available. And this position -- I would be slightly concerned with this position because it

doesn't address the issue that, in fact, there are now multiple effective treatments which may confound the ability to detect survival, and there already are other established endpoints short of survival to justify approval.

Thank you very much.

DR. WILSON: Thank you.

I'd like to open it up.

We've had Dr. Donohue join. If you could just state your name and where you're from into the record, please.

DR. DONOHUE: My name is Timothy Donohue. I am a urologist at the Walter Reed National Military Medical Center.

DR. WILSON: Great. Thank you.

Questions to Presenters

DR. WILSON: So let me start out by saying that I always have trouble, especially in a setting like this, of endpoints that don't either improve survival or quality of life. And I recognize that subsequent therapies can impact survival in any randomized study; however, that subsequent therapy

will be available to both arms.

So I guess my question would be regarding whether or not time to metastatic disease, which would be essentially bone, whether or not that is really a reasonable endpoint.

So as we get more sensitive in our ability to detect bone disease, I think we're essentially moving the clock. So the time to getting symptomatic disease will probably get longer. However, with currently used methods, be that regular PET, although I understand fluoride is now being more commonly used, what is the median range of time that it takes from the first radiographic or nuclear medicine detection of bone disease and the development of either symptoms or nodal disease, or other harder endpoints where you could really hang your hat on it?

I open it up to both of the speakers.

DR. SCHER: That's an excellent question and one that, obviously, has to be addressed. I don't think we know that consistently, because we do not have a good way of tracking disease tempo in bone

systematically. These are the type of investigations that are ongoing. But I think that's a key question as we're trying to understand at what point can we reliably predict that a change in a bone image will, in fact, portend for a clinical event that's unequivocal.

DR. WILSON: I think that's a real issue when considering that as your endpoint, because, again, we're getting more sensitive methods, I understand, to pick up bone disease.

Traditionally, for regulatory approval, we've wanted to see an improvement in overall survival or quality of life, and I think we could all agree that delay in symptoms is a real quality of life issue.

Whether or not one wants to include PSA anxiety in that, I don't know. I personally wouldn't. I just think that that is not a long-term endpoint. It's actually a reason to start drug. So I don't think we can really do that.

But what about this rather odd endpoint where you had a randomized trial, where the

endpoint was overall survival or time to symptomatic disease?

Now, we all recognize that if the bony disease shows up, nobody is going to want to continue to treat the person on that drug. However, they are open to use standard of care. And so the endpoint really -- so what this would require is the trial would continue beyond the period that they were receiving whatever randomized arm they were getting. So that we then saw what the subsequent time was to symptomatic disease as being a true, hard endpoint and not just using a -- we would record the nuclear medicine changes, but that wouldn't be the endpoint.

I'm curious what the speakers think of that endpoint.

DR. SCHER: I seem to be the lucky one. You're allowed to speak.

Again, if we knew that the tempo -- if there were data available that would show first occurrence, and those patients were tracked, whether on protocol or off protocol,

systematically, where you could clearly show that relationship, I would argue that is essentially what I was proposing by emphasizing the importance of not stopping the imaging and the follow-up in the patients as they continue beyond treatment.

Too often, the first clinical event happened, whether it's a PSA or a bone scan change, is the trigger to stop everything and then you lose that information.

The other point is there are patients who will be on -- again, I hate to use anecdotes, but if you have a patient who has 25 bone lesions and has been on a treatment for a period of three or four years, and then all of a sudden there's one new lesion in a sea of plenty, I would be hard-pressed to discontinue that patient, as well.

So your point is well taken about continuing that treatment to really understand the disease trajectory, and I think that's part of the reason why we have not been able to demonstrate a reliable association between progression as we have defined it and ultimate survival, which would, again, place

everyone in a much better position to say that this is clinically important, meaningful, and, therefore, we should not only act upon it, but it would be a basis for approvals.

DR. NELSON: So I was just involved in a study with another endothelin receptor antagonist that allowed patients to get standard care in addition to the therapy as long as there was the belief that the therapy was continuous.

This was not the design in phase 2. So it was a different design in phase 3. And the net effect, frankly, was that the placebo arm lived much longer than anybody would have anticipated, because you were applying effective therapies.

It also generally assumes the application of subsequent therapies to an experimental therapy are going to be equal, and that is a huge assumption. So although it makes it much easier to enroll patients into a placebo trial where you say to them, "I'm going to allow you to have any other approved therapy in addition to what you're getting here, and we're going to follow you to some

endpoint," frankly speaking, I think it's a leap. And, unfortunately, the trial I'm referring to was a negative for its primary endpoint, even though there was a slight difference in time to overall survival.

DR. WILSON: Okay. Thank you. Just to clarify, I think all I'm really saying is very simple, that the endpoint would be time to symptoms, irrespective of whether or not they still stay on the drug or not; so simply changing what your endpoint would be.

Dr. Armstrong?

DR. ARMSTRONG: So I'm going to be a little heretical here and raise the issue. I know that true adjuvant trials have never been done in prostate cancer, because you didn't really have much to use except androgen deprivation therapy. But sort of almost thinking about moving a little bit earlier with the fact that you now have four other non-hormonal agents approved, are there any trials going on of true adjuvant therapy, sort of not even for the PSA rise, and presumably looking

at the patients who are high risk?

The things that you've defined as high risk when someone's PSA rises are probably also high risk for having a PSA rise after initial therapy. Am I right or wrong about that? I mean, Gleason score, androgen receptor, KI67, the T score, those are bad when your PSA rises, and they're probably also predictive of whether your PSA will eventually go up; correct?

DR. PENSON: I'll handle that one, as the urologist in the room or one of the urologists on the panel.

So we have had some adjuvant trials immediately after both surgery and radiation. Obviously, adjuvant hormone trials after radiation are well known.

In the surgical world, we've had adjuvant radiotherapy trials which have been completed. When you look at agents, there have been two trials which have been attempted for adjuvant docetaxel in high risk patients, and both of them closed due to poor accrual, one in the community, which was

sponsored -- Adam Kibel was the PI. The other was in the VA. So the problem is we have a hard time getting those patients on trial. And, also, for the companies, the outcome is so far down the road that it's hard to get industry to sign up for those.

DR. ARMSTRONG: The other issue certainly -- and I'm sort of speaking to this as -- so I was thinking about the differences in what happens here when -- and I treat breast cancer, which is -- we don't continue hormonal therapy when it's failed. And in the adjuvant setting, we have data that combining hormonal therapy with cytotoxic, actually, you sort of have antagonistic effects.

So this whole concept -- and, Mario, you know, like, when I'm seeing prostate cancer patients with the fellows, like, why are you continuing something if it wasn't working. Is it the broken arrow effect, which is that if you actually -- it's rising, but it would be rising faster if you didn't continue the therapy.

Is there data on that or is it just that the idea of stopping what you've used as -- causes more of the PSA anxiety in those kinds of patients.

DR. EISENBERGER: No. The data is old. But I think we might be -- if I may. I think we might be losing a little bit of focus here on certain things. First of all, when we say that early hormonal therapy does not prolong survival, in reality, we don't know because it's never been tested.

The models where this has been tested in the past involve patients in a different era, different time, different ways of managing, different compounds, if you will, and the paradigm is moving further and further and further. I'm afraid that at this point in time, we're not going to have the opportunity to assess the role of early versus delayed hormonal therapy, because we missed the opportunity and we're not going to be able to.

So that's an important consideration. We need to make that distinction. Not knowing doesn't mean it doesn't. So that's an important thing

here, I know, but I wanted point it out.

I would go one step further and say not knowing today, we probably will never know. And the reality is today is that we have some data coming from our own institution and saying patients who have a very short PSA doubling time will die of prostate cancer. Patients who have a short doubling time and develop metastatic disease, they will die of prostate cancer. These are retrospective analysis, but they're based now on close to 20,000 patients at different institutions. They're very similar.

Now, the one thing I wanted to point out is one example is if you look at a patient who has a PSA doubling time with three months or less, the median survival in that patient population -- which was first pointed out by Charlie Pound in 1999 and then Freedland did it in 2005, and then Antonarakis just updated that. The median survival is about 6 to 6 and a half years if you have a PSA doubling time of less than three months.

Then Danil Makarov looked at our data in

patients who Pat Walsh did not treat with hormonal therapy, and two did develop bone metastasis. So he follows them on a yearly basis and, boom, they develop one bone metastasis; no hormonal therapy, failed surgery , most did not receive radiation therapy and salvage. That was his practice.

The median survival, those patients who developed metastatic prostate cancer on no therapy following surgery is about 6 to 6 and a half years. That's exactly -- very similar. They're not head-to-head comparisons.

Now, Anthony D'Amico, as was shown here, showed immediate survival of patients to have a PSA doubling time of less than three months, 6 to 6 and a half years. The Southwestern College Group then did Maha Hussain's trial, which was shown here, compared the survival of patients that were entered all intermittent hormone therapy trial, which half of them received continuous hormonal therapy. And it compared to a trial that I did about 15 years ago, comparing hormonal therapy plus or minus flutamide. The median survival now is a lot

longer. It's very similar to the 6 to 6 and a half years that we see.

So the PSA doubling time really describes the patient population, even though they have no metastasis, they're very close to the radar screen. It's popping up. And I don't see how one would not treat him with hormone therapy today. If you're sitting in the clinic, like I do, and the patient comes in and her PSA is 1 and three months later that PSA is 12, how can you not treat that patient somehow? It's not just a patient PSA anxiety. It's everybody's PSA anxiety, but it goes beyond that.

So it's a fact of life. We're dealing with a group of patients who started hormonal therapy, who now have a rising PSA. So we need to then talk about what to do with that.

Now, the one thing that's very interesting is -- that I find very interesting is the proportion of patients who come into our practice today, to the clinics today, in general, with bone metastasis are in pain. Any symptom associated

disease has decreased substantially. We're having a substantial degree of difficulty in actually doing pain studies. Isn't it possible that the practice of early hormonal therapy has altered that course, as well?

So I'm thinking about something maybe a little bit more out of the box. I turned around, not that recent, just looking at this and saying hey, it's a fact of life. We probably have now -- I estimate about half a million men walking around out there getting hormonal therapy with a rising PSA; half a million men, I'd say.

So what do you do with that? Well, some of them you may not have to do anything, but if they have a short PSA doubling time and they will develop bone metastasis, they will die of prostate cancer.

So why not consider the evidence of a reasonable evidence of bone metastasis in these men or any evidence of real progression? If you'll enrich your patient population for high risk as a reasonable endpoint for a clinical trial -- we

can't look at survival. We're even losing more of an opportunity now that we have more and more compounds that have been approved in the past year, and, hopefully, hopefully, another four coming in the future, because the field is very busy.

Why not just focus on patients who have castration-resistant prostate cancer, are at high risk, develop bone metastasis? It's bad. That patient will die of disease.

So, I'm sorry, I've been a little too winded on this.

DR. ARMSTRONG: But I guess my issue is that if you give that patient androgen deprivation therapy and they -- and maybe it slows down and then it starts back up again, and now they have a doubling time of less than three months, you don't stop. You keep them on that therapy. To me, that doesn't make a lot of sense.

DR. EISENBERGER: Now, the old studies showed that one -- the old retrospective data show that patients who stopped hormonal therapy actually would live shorter than those that would have the

hormonal therapy continuous.

We did that in the Southwestern College a few years ago and found very little difference. But it's very retrospective and has a long-term patient population.

One thing is the androgen receptor signaling process changes with androgen deprivation substantially. The molecular changes that you would see there, I would expect the PSA doubling time to become even shorter, because there is amplification and sensitization of that response mechanism, even a low testosterone that was.

So I don't know for sure, but I would anticipate looking at intermittent or hormonal therapy data, that PSA doubling time was short even further and will make it even more difficult to even consider this maintaining hormonal therapy in these patients.

DR. WILSON: Okay. Thank you.

Dr. Kelly?

DR. KELLY: Thank you, Dr. Wilson. I just want to make a really subtle point to begin with,

but it actually formulates the question a little better. It's more about semantics here.

We're calling this non-metastatic castrate-resistant disease. The problem is this is non-radiographic detected disease, and that's an important point as we look at endpoints, because you do have local recurrence and you do have metastatic disease. By definition, if you have surgical resection and a rising PSA, you have metastatic, but it's non-detectable by radiographs.

So the real question is when we treat prostate cancer, we look for things that will -- we pull the trigger to treat with. And we look at rapid PSA doubling time, symptoms, and change in radiographs.

So going back to your question, Dr. Wilson, if you had change in a bone scan, it would trigger a change in therapy. That change in therapy typically has increasing symptoms associated with it. So if you are going to the next level, have an increase in symptoms from your treatment, that is a clinical benefit if you delay that.

So we have to think about what is driving our treatment, and definitely change in bone scans, change in radiographs, change of treatment, and it's going to change the quality of life for that patient, because the treatment is going to change for them.

DR. WILSON: Well, I think that's a very good point, but a radiograph -- if our sensitivity is getting greater and greater using fluoride, we may end up calling the people progressive disease and something that really has no meaning. So I'm just trying to come up with something that really is a hard endpoint; that is, something that's clinically meaningful.

Dr. Raghavan, you had a question?

DR. RAGHAVAN: Well, really more a comment. I think there are a couple of other variables that we should talk about in this discussion, one of them being what do we mean by non-metastatic.

The other question that we just need to think about is what do we mean by castrate-resistant. There are so many different definitions

of so-called castrate-resistant disease. There will be cutoffs of testosterone at 50, 30, 20. We know that there's up regulation of androgen receptor function in the chronically castrated stage.

The other thing that hasn't been mentioned, and I'd be interested in Dr. Scher's opinion on this item. We know that very substantially in the prostate patient population, there is vast use of alternative medications, some of which are pro-estrogenic, some of which are actually pro-androgenic inadvertently. And I think one of the things we need to be thinking about for the future design of these studies is whether, in fact, confounding variables, such as alternative medications, will confound the definition of castrate-resistant.

I think the other fact that's important to understand is that despite all the information we have, there are always conflicting sets of data. My esteemed colleague, Dr. Eisenberger, made the comment that there are studies from the past that

show the discontinuation of hormonal therapy can be an adverse prognostic function. And I would quote that there are also studies that show that discontinuation makes no difference at all. In the series of studies from Portugal and elsewhere, in the SWOG trial, where patients have had continuous versus intermittent therapy, there's been a vast heterogeneity of impact.

In the adjuvant studies that have been done, there's heterogeneity of impact. We shouldn't forget the British MRC trial that's now dated and clearly was flawed of treating patients early versus late with hormonal therapy for asymptomatic bone metastases. And while it was reported, I think incorrectly, as a positive trial in favor of early intervention, and it was true that the British were able to show less legally related events, the overall survival was precious different, and that was in the PSA era.

So the point is there's a continuum of disease and much of that continuum suffers from lack of definition.

DR. WILSON: So, Dr. Scher, did you want to comment, as you were asked to?

DR. SCHER: Again, the consensus definition that was developed for castration was less than 50. That obviously has to change as more sensitive assays are becoming available. It's now known if one looks actually at intratumoral androgen levels, they could be very different than what's measured in the blood. And the more sensitive assays are using mass spec technologies, and there's an effort to standardize those so they can be applied in a CLIA-type setting.

At the same time, if one looks at the results with recently-approved abiraterone, that's known to further reduce androgen levels by at least a log in most patients, and that is associated with a clinical benefit.

So just to confound things further, there's actually data pre-clinically and some real anecdotal clinical data that testosterone can actually be therapeutic. So you'd really have whatever you want. The real issue is that the

androgen axis, if anything is hyperactivated, it's overexpressed in many patients, they're increased intratumoral androgens. We now CYP17 is up-regulated. There are mutations that can occur, co-activators, and, clearly, what we need to do is ferret it out which mechanism is driving which tumor so we can better appropriately pick the right treatment for the right patient.

DR. WILSON: Dr. Kelly, you had a comment.

DR. KELLY: I think Dr. Scher answered that. You just have to be careful when you look at these trials. The androgen levels have not been well followed when you look at these intermittents or stopping the trial. So we really don't know if you stop hormonal therapy, what kind of population we're dealing with. So those trials in Europe, in other words, did not follow that. So we have to be very careful how we interpret that data.

DR. WILSON: Okay. Dr. Sekeres?

DR. SEKERES: Thank you, Dr. Wilson.

Courtesy of Dr. Kelly and Dr. Raghavan, I had this moment of clarity, kind of like Ralph

Waldo Emerson describes.

As a hematologist, it sounds like we view chronic leukemia -- and I would lump into that CLL and myelodysplastic syndromes -- in a similar way as this. But we have a good study to base our approach to therapy on, and that is the New England Journal publication that randomized patients with CLL to initial therapy versus delayed therapy and showed no difference in survival. Therefore, we have to have the mettle to watch our CLL patients as their white count rises into the hundreds of thousands, as long as they don't require transfusions or aren't symptomatic.

Is that just simply not the case with this type of prostate cancer? In other words, is there a need for clinical trial design number 2, where you randomize patients to initial therapy versus delayed therapy, or is the practice so varied that you have to have that kind of clinical trial design to change practice?

DR. RAGHAVAN: Well, my response is practices vary. Practitioners are varied. It was

interesting when we were trying to design the SWOG continuous first as an intermittent study. One of the hottest debate topics was when do you pull the trigger for the patient who's been on intermittent treatment and you're going to start again. And the crusty old veterans, like myself, were sort of opting in favor of PSAs of 50 or higher, and there were people who wanted to do it as soon as there was an upward trend, irrespective of cause.

I think the reality is, in the practice community and in the academic community, there is no homogeneity of opinion, and I think the reality is, as one looks at this population of patients, the really well defined hard data are very poor. And so it makes it -- I think the answer to your question is if one were trying to make decisions here in the utopian view or in the purist view, we need more trials to answer the question.

As has been mentioned several times, a very significant part of this is the advocacy community and the patient community that find it untenable to sit by and watch PSAs rise. And that may be a

function of the fact that we've educated them poorly. More likely, it's a function of the fact that there isn't unanimity among the medical profession. The urologists will tend to be much more PSA-driven than the medical oncologists. I don't want to open the can of worms, but let's all remind ourselves that we still can't agree on screening and the utility of PSA.

So that just trickles down at each stage of disease.

DR. SEKERES: So even though, as you both pointed out, by definition, a rise in PSA is metastatic disease, and metastatic disease, by definition, is incurable. And any therapy you offer at that point is only going to add symptoms to somebody who is asymptomatic. There are still people who will do that.

DR. KELLY: Yes. I agree with Derek. It's very heterogeneous out there. I spend most of my time talking people out of therapy than in therapy, and there's a lot of drivers which cause therapy, people to pull the trigger.

I think it's a little difference between academics and community. There's differences there, because sometimes it's easier to treat a patient than to talk to them about what would be appropriate.

But the end of the day is we do not have good data to really guide us, and I think that's the bottom line is we don't have adequate trials to really tell us what to do.

DR. PAZDUR: Could I ask a question? Is this PSA kind of psychology a phenomena here only in the United States, or when you're talking to your European colleagues, do they face the same issues, where they cannot continue therapy if the PSA is rising or patients would demand a therapy with PSA rising?

Is this just a U.S. phenomena or do you think it's a more generalized phenomena throughout the Western world?

DR. RAGHAVAN: I think it's more extreme in the USA by a long shot. I think patients will tolerate rising PSA in similar cultures, such as

Australia, Britain and Canada much more comfortably, and that may relate to the way the press approaches it. It may relate to the concept -- and I don't mean this lightly -- that in the USA, death is seen as un-American, whereas in many parts of the world, death is seen as just an endpoint of life.

So our whole culture medically relates to what you might call heat rather than light; in other words, activity translates into doing something good.

One of the sad realities of life that challenges us all the time is we spend more on health care in the USA than just about any other nation, but our outcomes are not better. The Scandinavians and many other places spend a lot less and have better outcomes.

Now, an easy explanation of that may have to do with the fact that we don't do as well clinically. Another explanation is lifestyles are completely different, and that explains it; stress is different and so on. It just adds confusion to

the discussion.

DR. WILSON: I guess I would say that the major reason for this lies squarely on the physicians. In CLL, as Dr. Sekeres said, we watch white counts go up, and patients don't worry about it because we tell them not to worry about it.

So the press picks up what doctors say, patients pick up what doctors say. We've already seen how there's a big reimbursement for this, and I'm afraid that this goes to the core of the medical system, and I think that there are a lot of doctors out there that are simply pushing these drugs.

I would agree with Dr. Kelly that it is probably easier to give drugs than to simply watch, but I think if patients felt comfortable with watching, there wouldn't be the pressure.

Dr. Scher, you have a comment.

DR. SCHER: I just want to reiterate. Now, we do have prognostic tools and we probably don't use them as well as we should. If we can sit with a patient and say that "Based on your particular

pattern, nothing is going to happen for you clinically for four or five years," that's a very different discussion than saying, "Look, we've looked at your numbers and your prior treatment history, and you have a high probability of an event in two years," that's very different.

This started in my practice with the first question of "Should I rent the condo in Florida," and most of the time I would be very happy to buy the ticket. But once you instruct that you can inform the patient of their case, not just the totality of prostate cancer, most patients will listen.

In point of fact, the -- well, the second component of that is they need to understand that a rising PSA means that the absolute number will go up, but, in fact, it's not -- there is no rate change, so that there has been no change.

But I agree with Kevin, we shared practices for quite a while. In point of fact, you spend more time talking patients out of treatment than you do actively treating. But, again, if you see

the rapid rising PSA six months, nine months, that's a very difficult patient to sit on the sideline. That's the patient you want on trials.

DR. WILSON: Dr. Garnick?

DR. GARNICK: I have several comments. First, I'd like to congratulate Dr. Pazdur and yourself for bringing this topic to this sort of forum. It's something that is totally perplexing. There's tremendous ambiguity, and there are clearly no clear-cut answers.

But I understand you're trying to ask us to address the design of clinical studies, assuming that the patient has been on hormonal therapy and is now refractory to hormonal therapy.

That's the -- okay.

I would also like to say that the use of androgen deprivation for the rising of PSA in the primarily treated patient with either radiation therapy or radical prostatectomy is very, very uncertain. It's commonly done, and even the criteria that justifies its use and its continuation in the development of non-metastatic

castration-resistant prostate cancer is very uncertain to begin with.

The issue of assessing quality of life, especially when the downside of having a skeletal-related event is very, very important, but I don't think there's been enough emphasis on the quality of life issues associated with continuation and initiation of androgen deprivation therapy to be begin with. And many patients will tell you that losing their potency or losing their vigor is far worse than having some pain. And I think that then is some sort of composite assessment of SRE-related QOL can be compared to ADT-related QOL needs to be assessed in any sort of long-term issue.

The other thing is that the continuation of ADT, it's commonly done. Obviously, in the patient that's been orchiectomized, that's not a consideration. But for the patient on either a GnRH agonist or antagonist, it's less clear what the long-term effect is on continuation of ADT.

It's known, for example, that patients continue to get their Leuprolide or their

Goserelin, despite the fact that they are castrate-resistant, and many of those patients who have been on therapy for greater than a year or so actually have tested uro-atrophy. So the likelihood of those patients ever recovering their normal hypothalamic, pituitary, gonadal function is very, very small, and we continue to give them injections of therapies that may have non-physiological side effects.

So those are, I think, the very important issues that the FDA would face in trying to determine composite endpoints.

Just one or two other comments. In my own -- we've sort of assumed that when a patient's PSA goes up, the post-radical prostatectomy radiation, that this implies micro-metastatic, non-detectable, not yet diagnosable prostate cancer.

I would urge that in any trial design, that the evaluation of the prostatic fossa be done either with anastomotic biopsies or endorectal MRIs to make sure we're not missing a local recurrence.

There are also incisional abnormalities

during radical prostatectomy that actually leaves prostatic tissue behind, which, several years later, can cause elevations in the PSA. That has nothing to do with either metastatic disease, but just basically represents a continuum of prostate tissue.

In the radiation patient, for example, our typical protocol for someone that, quote-unquote, "has a rising PSA following radiation therapy" is to basically do an evaluation of their prostate gland and, if biopsiable, try to identify and demonstrate a local recurrence, and then treat that patient with some sort of salvage therapy as opposed to throwing them into a mix that has metastatic disease.

The final point that I want to make is that there's been no mention of monitoring of testosterone values in the diagnosis of castrate-resistant prostate cancer anywhere between 2 and 3 percent of patients on, quote-unquote, "hormonal therapy" will actually have non-castrate levels of serum testosterone by either virtue of M mutations

in their LHR interceptor or pharmacokinetic abnormalities in their use of the particular depot.

So all those things I think need to be incorporated into some sort of trial design, in addition to what else is discussed.

DR. WILSON: Dr. Loehrer?

DR. LOEHRER: Mainly because Derek is here, I have some random thoughts, I think, that I just wanted to -- he makes me do this. But the discussion about -- actually, Debbie brought up the fact about breast cancer. I'm also thinking about physicians, in general, with patients coming to the emergency room with runny nose, fevers, muscle aches. We know antibiotics is the wrong thing to do; yet we do this. Similarly, with sinusitis, we know antibiotics don't make a big difference, but we do this because it's easier. I think many times it's a lot easier, far easier to treat than it is to have this discussion.

The door was opened up by Dr. Nelson, and I would like to have maybe him and some of the other people comment on this, about cost and

reimbursement. I know the FDA is not supposed to talk about this, but, again, the door was opened up.

If the patient is coming in with their PSA rising and want to be treated, and if a physician then treats them, and yet he also gets reimbursed for this practice, it seems like the system is set up to treat more people than probably are needed.

I wonder, again, following up on this question -- maybe Derek can talk about that -- in the European system, where the reimbursement is different, is that a driver in terms of some of some of this, in terms of over-treatment?

That's one question. And then the other part I'll ask, or comment, is following up on Marc's, is that we have a tendency, I think, in physicians, even in their own personal lives, "is it my fault?" And when a patient dies with prostate cancer or any other cancer, we kind of want to know if it's our fault, and we look at prostate-specific mortality being lower and we feel a little good about ourselves.

If they died for other reasons, because of cardiovascular disease, which is questionable -- or other factors, they're just as dead as if they died of prostate cancer, and I think it does -- to Marc's point, we need to carefully look at the long-term side effects, much like we did in some other drugs that have been looked at by this committee. And a modest impact of potentially lethal side effects are worthwhile, and we need to pay attention to them.

But I would -- since the door has been opened -- I don't know. Do we have a thought on the European side of things with reimbursement?

DR. NELSON: I can't comment about the European side, since I'm an American, but I can tell you that the OIG, on the second reduction of LHRH agonist to patients who are on Medicare has made it at 106 percent of basically cost, and you get 6 percent, which almost doesn't cover the expense of delivering it in your office.

So the trend actually has been to try to spread out the times the patients come in. So

depots that have gone from one month to three months, now people have modeled this and said it's probably better to do it every four months, because we almost lose money having the patient come in.

So I think the incentive, financial incentive, has been removed largely from the administration, at least in Medicare patients.

DR. PAZDUR: Just a disclaimer here -- criticism of this committee. The FDA does not consider cost of therapies, et cetera, into any trial design or any regulatory decisions. Just to circumvent things.

DR. WILSON: No. I think that's a very critical key. But I think much more important than cost is if these drugs are not benign, if we're not improving quality of life and we're not improving survival, we have no business giving them.

So far, from what I've heard, is we don't have any randomized evidence that giving these drugs early helps. We have a lot of we're worried about what's going to happen or they're going to die in six years.

However, again, being a hematologist like Dr. Sekeres, we have faced this in lymphoma. And contrary to what everybody would have said, it turns out that early treatment with known disease, even widespread, doesn't help one iota. And with that, I'm going to ask Dr. Sekeres to make his comment.

DR. SEKERES: Thank you, Dr. Wilson.

I just wanted to ask if Dr. Scher could clarify something that you had said earlier. It seemed as if you were saying, gee, it would be a good thing if we identified these folks who have high risk of badness occurring in the next couple of years, like PSA doubling time of three months after their prostate has been removed, and that those folks we would potentially intervene on.

Is that correct or am I misparaphrasing?

DR. SCHER: No. That's the exact design of our therapeutics program. We restrict our aggressive treatment approaches to patients with rapid doubling times who have, in fact, had a radical prostatectomy and, ideally, have had their

pelvis radiated so there's no local disease.

DR. SEKERES: And I don't know if I missed it, again, and I apologize if I did. Did you show a study that shows an advantage to intervening early in these folks you would consider higher risk?

DR. SCHER: Well, they're randomized trials with radiation treated patients, plus or minus as short as six months of hormones, where there's been a clear survival benefit shown. So there is efficacy of hormonal therapy in early stage, we would argue, minimal disease, post-affinitive local treatment, which is a rationale for trying to be more aggressive in those declared aggressive localized tumors that have recurred before they have established metastatic disease, recognizing that they are micro-metastatic.

DR. SEKERES: So I'm aware of this study that just came out that showed that. But there's no similar study in patients who have undergone prostatectomy who then get early intervention with hormonal therapy.

DR. SCHER: There have been studies -- I mean, there have been studies which are showing delayed metastatic recurrence. There was a New England Journal publication of patients who had proven nodal disease, arguably, high risk, which, although potentially underpowered, also showed a survival benefit.

So there is efficacy data in minimal disease settings which clearly shows that you can affect survival. The idea there is a definitive treatment period and stop. It's not prolonged. It's not lifelong therapy.

DR. SEKERES: Okay. And by minimal disease, you mean --

DR. SCHER: Well, presumably, microscopic, because, again, the patients in the radiation series are getting concurrent hormones in treatment. So the PSA measurement is essentially not reliable to say, again, whether it's metastatic; we'll presume that some of those are. They're high risk by the various -- some of the various definitions based on Gleason score, T stage

and PSA at entry.

DR. SEKERES: I'm sorry, but we keep circling back to this. It's just such a different approach to disease than those of us who treat he malignancies that are chronic, where --

DR. SCHER: It actually isn't, because there are certain prostate cancers that are declared aggressive. Similar to CLL, you have some patients who have declared themselves as aggressive.

For the more indolent disease, which we can track now, we tend or we try not to intervene with toxic treatments and try to have patients understand that their risk of morbidity and mortality is low and they should get on with their lives and enjoy the fact that they don't need treatment for their cancer.

DR. PAZDUR: Do you think that reflects, Howard, just treatment at Memorial Sloan-Kettering, or is that a general paradigm throughout the United States? Because here, again, we hear different things from sponsors that come, much different from what you're telling us.

DR. SCHER: Well, you have representatives from east coast.

DR. RAGHAVAN: Well, in the south, it would be very similar. I think we are increasingly trying to identify the bad actors, because there's actually a serious chance of demonstrating benefit. If you confuse the issue by having all comers with rising PSA, it becomes incredibly difficult to show a true biological impact.

I think one of the things that is important is that all the surrogate endpoints in this context really do still remain to be proven, and I think Dr. Scher made a very important point earlier, which is you really, in these sort of studies, want to be anchoring them with survival.

At the end of the day, given the fact that you get a second bite at the cherry and a third and so on, the fact that abiraterone and some of the newer generation second-line hormonal therapies can do so many different things and delay time to progression. They can also alter the hormonal milieu.

I think one of the things that I hope we get out of today is that we don't only focus on surrogate endpoints. If we finish today by identifying a cadre of bad actors with rapidly rising PSA, my guess, if you went around the cancer experts in the room, they'd all agree that something like a less than six month, less than three month doubling time is a reasonable criterion for patients that will do badly, and then to find that you could have time to progression, but that you anchor that with overall survival, because there have been many studies where something has been introduced at the time of progression, but survival at the end has evened out.

So my plea for today would be to ensure that we don't lose the overall survival endpoint.

DR. EISENBERGER: I just want to point out something exactly to that. When I mentioned the high risk patients, I mentioned that it would probably be somewhat -- well, maybe that represents 20 or 25 percent of the entire patient population with biochemical relapse following local therapy,

at most.

Most of the others, including -- there was an observation in our own data, is that we'll not die of prostate cancer. We estimate their survivability to be way beyond several years, and, in fact, Freedland showed that, that the risk of dying of prostate cancer increases or the risk of prostate cancer mortality becomes really more significant with PSA doubling times of less than nine months.

So I think that there is a tendency today of not treating good risk patients. I think that's what I would say. And the issue of whether to treat or not poor risk patients, I believe it's unresolved.

But the point I was going to make is that it is a fact of life, and many of these patients are receiving hormonal therapy at this point. And it is the poorest patients who frequently come into the oncology clinic with a rising PSA and a castrate brain. So this is -- I hope we don't lose focus of that. This is the patient population that

we may know a little bit about and we probably should do clinical trials.

DR. WILSON: Actually, we're going to go ahead and take a break, because we're going to have plenty of time to go on with this discussion. But, Paul, you had one comment , and then we will go ahead and keep your names on this list, and after we have the open public hearing, we will resume this.

DR. KLUETZ: I just wanted to make a quick point to try to get people focused back way from early versus delayed androgen deprivation therapy. My goal kind of -- and it ended up being a large part of my talk. My goal really was to show that there isn't very good data for it, and to show how the population is now here.

With respect to the use of early versus delayed androgen deprivation therapy, and my research that I have done, there's two ongoing trials, large trials, outside of the U.S., ELAAT and T-R-O-G. I spoke with Dr. Duchesne, who is the primary investigator for the TROG trial, and even

in non-U.S. sites, they're having a very hard time accruing to early versus delayed, which would have perhaps answered this question.

In fact, of the ELAAT trial, she said something around 70 patients out of 1100 had been accrued, and the TROG study was going to be closed for lack of accrual, too, with one-third of their accrual.

So I think while we don't condone the off-label use of androgen deprivation therapy, it is a clinical reality, and I'd like to try to focus the conversation to the study and non-metastatic CRPC for the rest of the afternoon, because I think that's probably enriched anyway, as you all say, because, hopefully, people are starting to use predictors now to initiate ADT.

They're already moved farther in the disease setting anyway because they've been on hormones for a while. And so I think this is the population that we're going to study, I hope. Thank you.

DR. WILSON: Okay. Why don't we go ahead and take a short break? And right now it's

approximately 3:15. So at 3:25 we will reconvene.

Thank you very much.

(Whereupon, a recess was taken.)

DR. WILSON: Okay. If everyone could start taking their seats so we could go ahead and get started, that would be great.

Open Public Hearing

DR. WILSON: We are now going to be entering the open public hearing portion of the meeting, and I have a statement to read.

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

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

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

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where each participant is listened to carefully and treated with dignity, courtesy and respect. Therefore,

please speak only when recognized by the chair. Thank you for your cooperation.

I would now like to invite Mr. Williams to the podium.

MR. WILLIAMS: Thank you, Dr. Wilson. And thank you, for the entire committee, for the opportunity to share my public comment with you all today.

My name is Scott Williams, and I'm vice president at Men's Health Network. I'm actually here today speaking on behalf of the Prostate Cancer Roundtable, which is a group of 12 independent patient-centric, not-for-profit organizations that cooperate through a national policy agenda to support high quality prostate cancer research, the prevention and early detection of clinically significant prostate cancer, and the appropriate care and effective treatment of men with prostate cancer, major improvements in the therapeutic options for men with progressive and advanced forms of this disease, and the appropriate education of all men at risk for this disease.

Our fundamental priorities are to ensure that over time, we all work together on scientific, political and social priorities that will lead to a major decrease in the incidence and prevalence of clinically significant prostate cancer, the early diagnosis and optimal treatment of all cases of clinically significant prostate cancer, and access to high quality care for all men diagnosed with this disease. We appreciate the opportunity to share our perspective with you today.

When it comes to endpoints, it's not always about overall or disease-specific survival. To make progress in the management of earlier stages of prostate cancer, we all understand that we need validated endpoints that reflect real clinical benefit to patients, even when a therapy may not extend life.

Other than survival, there are no current FDA-approved endpoints for clinical trials of prostate cancer in treatment of men with non-metastatic castrate-resistant prostate cancer or with hormone-sensitive, but non-metastatic disease.

There appears to be at least one clearly establishable surrogate endpoint for progression of men with non-metastatic CRPC. That is the appearance of evident bony and/or visceral metastases that can be clearly identified on bone or CT scans. And we note that denosumab does appear to delay the appearance of metastases to bone in men with non-metastatic CRPC.

We're aware that through the DOD-funded Prostate Cancer Clinical Trials Consortium, a proposal has been made to the FDA for the consideration of other endpoints within the approval process. A team has made a presentation to the FDA for modification of their protocol, and that dialogue is ongoing.

We look forward to the results and want to contribute to be a part of the process, the dialogue, and consideration. We believe it's very important to distinguish clearly between the occurrence of potentially clinically significant endpoints that might reasonably be expected to change the management of a disorder, for example,

the visible appearance of mets, and clinically less significant endpoints that would probably not change the management, for example, an increase in the number and size of mets.

We encourage the FDA and the sponsors of new treatments for prostate cancer to work closely with the Developing Patient-Centered Outcomes Research Institute, or PCORI, to support the development, validation and subsequent application of primary and secondary endpoints that are highly relevant to assessment of benefits and risks that are really meaningful to patients with progressive forms of prostate cancer who need new and improved therapeutic options.

Thank you very much for the opportunity to provide the public comment.

DR. WILSON: Thank you. Thank you very much.

I would now like to invite Dr. Smith.

DR. SMITH: My thanks to the agency for this opportunity to comment. My name is Matthew Smith. I'm a prostate medical oncologist and the program

director for genitourinary malignancies at Massachusetts General Hospital in Boston. I'm representing myself, and I have no disclosures. I have three points to make. I have seven minutes, and I will try to make them clearly.

First, in men with non-metastatic CRPC, continuous androgen deprivation therapy is the standard of care. Second, concerns about cardiovascular adverse effects of ADT have been overstated by the medical and non-medical community. And, third, high risk, non-metastatic CRPC can be readily defined and represents a deadly disease state.

CRPC is defined as disease progression, usually a rising PSA, despite current ADT. In contrast to the ODAC briefing book, though, men with non-metastatic CRPC often have initiated ADT for one of several reasons, not just a rising PSA, and some of these common indications are shown here.

In some of these settings, ADT has been shown to improve overall survival. In other

settings, the optimal timing for initiation of ADT is undefined. For many of these men, though, it's really not a question of if, but when they'll initiate such treatment.

While the best timing for initiation of ADT may be controversial, the continued use of ADT in men with CRPC, metastatic or not, is not controversial. Continuous ADT in men with CRPC is the standard of care and part of the NCCN recommendations for management of this disease state, as shown on this slide.

Whether continued ADT improves survival is unknown. Absence of evidence, though, is not evidence of absence. We do not and will not have high level evidence regarding the impact of continued ADT on survival because most would consider it unethical to discontinue ADT in this setting.

Risk-benefit considerations are central to all decisions about treatment, but the concerns about cardiovascular adverse effects appear to have been overstated by, again, the medical and non-

medical community. ADT has a variety of potential adverse effects, including osteoporosis, sarcopenia, and obesity. Large population-based studies have consistently reported that ADT is associated with greater risk for clinical fractures and diabetes. The relationship between ADT and cardiovascular disease, however, is far less clear. A comparison of results between diabetes and myocardial infarction outcomes may help make this point.

Using SEER Medicare data, our group first reported that ADT with GnRH agonist was associated with greater risk for diabetes and myocardial infarction. In contrast to diabetes, though, the link between ADT and myocardial infarction was not consistent for different forms of ADT. We saw it in the case of GnRH agonists, but not with bilateral orchiectomies.

Similarly, the relationship between ADT and myocardial infarction has not been consistent between different studies. Three large population-based studies are represented here. You'll see a

consistent relationship between ADT and diabetes in each of these studies. That was not the case for myocardial infarction.

Further, if the relationship between ADT and MI is causal, the magnitude of this risk appears relatively small. Using data from our SEER Medicare study, for example, their estimated number needed to harm for each excess MI was 384. That number is similar to the number needed to treat for statins when used as primary prevention. In other words, the risk of ADT, if causal, appears no greater than that associated with withholding a statin in a patient at low risk for cardiovascular events.

Most importantly, nearly all studies have observed that ADT is not associated with greater cardiovascular mortality. Specifically, all the largest studies with the most informative events have reported that ADT is not linked to greater risk for cardiovascular death.

Concerns about the safety of ADT are warranted and should be center stage in decisions

about initiation of ADT, particularly in settings where optimal timing is undefined, including the rising PSA setting. These concerns, however, should not interfere with the appropriate use of ADT in other settings, including CRPC, metastatic or otherwise.

In 2005, in an attempt to understand the natural history of non-metastatic CRPC, we analyzed data from the control group of an aborted clinical trial designed to prevent bone metastases. All men had a rising PSA despite ADT and no evidence of bone metastases at baseline. Despite standard of care, including continued ADT, one-third of men developed bone metastases after two years, and median bone metastasis-free survival was about 30 months. Notably, higher PSA and faster PSA doubling times were the only baseline factors associated with worse clinical outcomes.

Bone metastasis-free survival is shown here, according to tertiles of PSA in the left and PSA doubling time on the right. PSA doubling time and PSA have now been validated as markers of adverse

clinical outcomes in men with non-metastatic CRPC.

We recently completed a global, randomized, controlled trial of men with non-metastatic CRPC, defined as high risk for progression based on a PSA greater than 8 or PSA doubling time less than 10 months at baseline. These criteria correspond to roughly the top half of risk groups.

In the placebo-control group of this contemporary study, shown here, median time to first bone metastasis was 29.5 months, and median bone metastasis-free survival was 25 months. For most men, bone metastases were identified by scheduled radiographic assessments. Nonetheless, about one-third of men had bone pain at the time of initial bone metastasis diagnosis.

Nearly all men developed bone metastasis prior to death, consistent with the well recognized role of bone metastases in prostate cancer morbidity and mortality. Median overall survival was only 44.8 months, similar to the historical overall survival for men with bone metastasis at a time of initial prostate cancer diagnosis in the

pre-PSA era. Simply put, men with high risk non-metastatic CRPC have a deadly disease, and this disease state is a critical area of unmet medical need.

I applaud the committee and the agency for your efforts to address this important unmet medical need in a manner that will benefit all stakeholders, most importantly, our patients. Thank you.

DR. WILSON: Thank you. Thank you very much. This now concludes the open session.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the questions to the committee.

Is the FDA going to read these?

Questions to ODAC and ODAC Discussion

DR. KLUETZ: So we've designed a couple of

slides to reorient you to the issues for discussion. Next slide.

With respect to the patient population, we've asked the committee to discuss what population of non-metastatic PSA recurrent prostate cancer patients, both hormone naive and castrate, that are appropriate for trials intended to support approval of products in this population. I think we've done a good job of discussing that already.

If trials should be limited to those patients at high risk for prostate cancer morbidity and/or mortality, discus how high risk populations should be defined.

For issues with respect to trial design and endpoints, discuss the use of different study designs in asymptomatic non-metastatic PSA-only recurrent prostate cancer. Discuss endpoints to be used for each type of design. And for the trial design number 2, the immediate versus delayed study design that I suggested, discuss potential disease progression criteria to initiate delayed treatment.

DR. WILSON: Okay. Thank you.

Just for clarity -- and I don't know if others are as unclear as I am. However, I would like to get the feelings from both the experts on the panel, as well as our two esteemed speakers, to the following question.

Do you feel that, number one, it is standard to use ADT in low risk PSA-rising non-metastatic prostate cancer at the current time? My understanding is no. But I'd like to know what your feeling is on that. And number two, is this an area that we need to study?

DR. RAGHAVAN: I think that for each of us, this is going to be opinion. So for low risk disease, meaning long doubling time, asymptomatic, no clinically definable mets, I do not think it's standard of care to use androgen deprivation therapy, and I don't see this currently as an area of unmet need.

I would take the view that in an era where there are only so many resources, both patient-wise and trial-wise, I would focus on the group that Dr. Scher and I both talked about and Dr. Kelly,

which is the dangerous people. I think those with low risk disease have a long and variable natural history, where the potential for harm from intervention is not necessarily offset by the potential for benefit.

DR. PENSON: I'm a little confused, because I understood us talking about castrate-resistant prostate cancer, and we keep coming back to hormonally naive biochemical occurrences.

The question that was posed in the backgrounder was do we believe the trials of the M0 CRPC setting would increase the use of -- the off-label use, mind you, of ADT in hormonally naive biochemical failures. I'll answer that question, then I'll ask the panel to help me out here, or I'll answer your question about what I think the standard of care is.

My opinion is that it'll have no effect on the use of ADT in the biochemical recurrent setting because it's already going on, and that's a separate question. Dr. Scher had a slide that said they were independent questions. I think that we

can't link them together, because there truly is a need in patients who are M0 CRPC.

Now, you may be able to risk stratify between high and lowest patients, but those patients are coming to doctors' offices across the world saying, "My PSA is going up. I've been on hormones. This is bad, right, Doc?"

So in my mind, the question about what is the standard of care for a biochemical occurrence is moot, because it happens, it's not going to change. We've removed the financial incentive, which is good, because I think what drove it in the late 1990s, early 21st century was the money. But it still goes on.

I won't go into why that goes, Dr. Wilson, because I think it is partly to blame to the doctors, but I think it's much bigger than that. I don't think we can change that.

So I think we'll talk about the other pieces, but I just want to really reiterate the fact that the standard of care in the community is, yes, those patients get treated. Whether it's

right or it's wrong, I don't know, and it would be an extremely difficult clinical trial to pull off in 2011.

So I would echo the comments that we need to focus on high risk patients. I would define them as M0 CRPC patients, and then within that group, we could probably identify low versus high risk patients.

DR. WILSON: And so the other group would be those who are PSA-rising non-metastatic, but have a rapid rate of rise. Is that a group that needs to be studied?

I guess what I'm trying to do is I'm trying to figure out what other groups we need to be doing trials in, so we can then talk about what kind of trials and then what sort of endpoints. I know that many of you have already thought about this, have those trials, but I don't study this field.

DR. PENSON: The one thing you left out there in that comment was whether or not they were on hormones or not.

DR. WILSON: Well, I'm talking about there

is those that are on hormones that are rising. That's the castrate-resistant. I'm talking about people who have rapidly rising PSAs, hormone naive. Is that a group that needs to be studied, as well?

DR. RAGHAVAN: So, Wyndham, the analogy here, if I can switch Mikkael and you away from CLL, if you think about this population as being much more akin to CML when you see the first cytogenetic evidence of transformation and when you see your first few altered blasts with a completely different genotype coming up -- and we know that you can have 20 years of CML without treatment with high counts, and everybody is pretty comfortable. Then you see that genetic change come, and you know that you've got a short period of time.

So I think not a bad analogy is the patient who is on hormones and has had, for argument's sake, a slowly rising PSA with a doubling time that might be two years, and then suddenly, on a random visit or a program visit, you find a change with a big jump in PSA. That can be artifact. In clinical practice, you'd probably recheck that a

month later and it's confirmed, and now you know you've got a different situation.

I would make a plea -- and I think Matt Smith from the audience made a plea, and Dr. Scher and others have all said these are the ones that do badly. They get into trouble most of the time, and I think Howie has set the criterion of getting into trouble within two years.

When he does that, it doesn't make two years and four months okay and two years not okay. But as for the purposes of discussion, it's focusing us on an entity that will get our patients into trouble in a hurry and where the morbidity of intervention can be justified by the potential for gain for the patients.

DR. WILSON: Let me just one more time say for those people who are hormone naive, who either have rapid PSA rise or early PSA rise, is that a group that you all need to be studying, as well?

That's a group, too. So that's a separate group from the high risk castrate-resistant group.

Okay. Good.

Dr. Mann?

DR. MANN: Yes. First of all, about the question on hormone naive patient population, the most publicized study recently was done by the NCA Canada group, led by them, and that study looked at continuous ADT versus intermittent ADT. And that study started in, I think, '98. So the question whether there should be no treatment arm in that setting, nobody is even studying that.

The second point I would like to comment on is this issue of delayed treatment. Again, NCA Canada led a trial called -- it was called STAR trial, and it was a radical treatment right away in newly diagnosed prostate cancer patients versus delaying it at some sign of progression, which was going to by active surveillance measuring PSA or doing serial biopsies.

The study required accrual of 4,000 patients. CTAP very reluctantly agreed to conduct -- make an attempt at doing that trial. After about three or four years of trying, after accrual of only 180 patients or so over a period of

a good four years, that study had to be -- it was closed by the data monitoring committee. And I don't think that, myself, personally, I can have a lot of enthusiasm generated in the CTAP to do a trial of right away versus delayed treatment.

This situation is even worse in the setting where somebody has already failed ADT now, and it's driven by the patient, as well as by the physician. And delaying treatment is just difficult. So I don't think that the second design proposal is something which I would support.

Then I have a question here for the agency.

Could I have the last slide from Dr. Scher's handout stating agency position? And the second point on this says that the preferred endpoint of clinical benefit is prostate cancer-specific survival.

Is that really the agency position?

DR. NING: I don't think we specify prostate cancer-specific mortality as an endpoint. We are trying to continue to use overall survival in our briefing document, and we did not. I don't think

that's very right.

DR. MANN: Because there are -- in approval of any treatment, one issue is the efficacy, the other is safety. And when you are excluding all of these all other cause deaths, there is this big assumption made that there is absolutely no biological relationship between the disease and the treatment and these so-called other cause deaths.

So even if you can determine very clearly that this death is indeed not a prostate cancer death, which pulmonary embolism, which DVT and which MI, which stroke, which MDS, which acute leukemia is not related to your treatment, that is practically impossible to determine.

So even if one is to start looking at prostate cancer survival or any of these other endpoints or surrogate endpoints, you cannot censor other deaths, because all of these other deaths, they are going to be an issue.

So I'm glad that this is not the agency's position.

DR. NING: I'm glad that you point this out.

We basically want to clarify here that we'd still like to use overall survival at this point.

Another issue, actually, that's related to another point that Dr. Scher mentioned in his presentation, that delaying or preventing bone metastasis is a clinical benefit to patients.

That's the one I think that in our briefing document we specify that. We're basically concerned about asymptomatic metastasis. And at this point, I think that I would not have difficulty to understand if a product delays metastasis for a couple of years or for a few years with an acceptable safety profile. However, I do have a difficulty to understand whether a product that prolonged or delayed metastasis for a few months with considerable toxicity, that does not have any overall survival improvement.

So I'd just like to clarify here that we do not think delaying or preventing bone metastasis currently represents a clinical benefit.

DR. MANN: I think usually when you have overall survival as the primary endpoint, you are

usually overpowered for the progression-free survival type of endpoint. But all kind of this time to this or time to that, where you are censoring other cause deaths, those are not appropriate, because that basically tells you anybody who develops a toxicity is just not followed. So that patient in the survival curve basically benefits forever.

DR. NING: True. I agree. I think I'd like to make another point to that about the metastasis-free survival, because if you look at the trial that is the Zometa trial, an AstraZeneca trial, at two years, about 20 percent of the patients died.

Our analysis -- or we don't have data, but our estimate showed that possibly a majority of those patients had died of competing disease. So, therefore, metastasis-free survival may not be a very good endpoint either.

DR. WILSON: Dr. Kelly?

DR. KELLY: I wanted to clarify this a little bit, because -- and I'm going to call on Dr. Eisenberger, his database there.

If you're on hormonal therapies and has no metastatic disease started on it, and you develop metastatic disease, what happens to those patients in the Hopkins database? Do they die?

DR. EISENBERGER: Yes, that's a good point. High risk patients developed metastatic disease. Whether they received hormonal therapy or not, they will die of prostate cancer.

DR. KELLY: Okay. The other question is that looking at the database, how many patients -- let's look the other way. How many patients without metastatic bone disease actually die from the prostate cancer?

DR. EISENBERGER: Very few. I mean, it's very few.

DR. KELLY: Right. So the development of metastatic disease on hormonal therapy is a lethal phenotype. So that's an endpoint. Patients die when they get bone disease.

So if you prevent that, that data actually suggests that you're going to have an improvement in survival. So we just have to really -- I mean,

your statement there, you said if you don't develop a bone mets, you don't know if that's going to reflect a clinical benefit or not. But we know from the databases, if you develop metastatic disease in the bone, that's a lethal phenotype, correct?

DR. NING: True. I think if bone metastasis is detected, that would mean disease progressed. If you delay that, that would mean that treatment effect occurs. However, we have no knowledge how much delay in the bone metastasis would represent --

DR. KELLY: I understand that. But the question is just if you develop bone metastasis or not -- bone metastasis is a bad thing.

Do we all agree on that?

DR. NING: We agree, as well.

DR. KELLY: Okay. So the real question is what duration of prolongation would turn into a significant clinical benefit.

DR. NING: That's an uncertainty. We don't know. That's the reason we --

DR. KELLY: Right. But I think that we first have to start with the first step there, is bone metastasis is a bad thing, and I think we can all agree with that.

DR. KLUETZ: Well, I would like to actually have the panel discuss that, because it's still an unestablished surrogate with respect to the agency, whether time to metastases alone, asymptomatically, is an established surrogate for survival.

You were mentioning data that we haven't seen. And so that's one of the things we wanted to bring up; what would be a surrogate for survival in this disease setting? So we welcome the debate.

DR. WILSON: So, you know, this is no different than every other cancer out there. We know when breast cancer spreads, you die. We also know delaying breast cancer by three months, progression doesn't seem to affect how long you live. And so I think it's the same question that we deal with every time that we deal with metastatic disease. Nobody denies what's been said. But what we don't know is whether or not

delaying it by a few months is really clinically meaningful in terms of making people live longer or have a better quality of life.

I asked Dr. Scher what's the time between first radiographic appearance and symptoms, and they don't even know that. And so I think this is the problem. If you set up a clinical trial where your positive outcome is really a p value of less than .05 with a certain power, if you have a big enough trial, that may only be six weeks, and, yet, we may not be helping a single folk.

So I think this is the age-old question we face all the time. And so I think this is why we have to be very careful not to just assume that time to metastatic disease needs to be the endpoint.

I think you made the point, Min, that two years, I think we would all agree is probably a very robust number if we could delay it two years. But is it six months, is it one year? I don't think anybody really knows.

DR. NING: Definitely we have no data to

support that, whether it's six months or even a year delay in metastasis would be clinically beneficial.

DR. KELLY: I do agree that you don't know the timing, but I think the first step we have to say is metastasis is bad. And I think that we first have to recognize that that will lead to death.

DR. EISENBERGER: I hate to say this again. We are losing a little bit of the focus. What the first question is here, not knowing the answer doesn't know it isn't the case. And I think there's a huge difference between the hormone naive versus the castrate-resistant. I think the hormone naive, even in the high risk patients, I think the question of whether any therapy makes a difference is not an unreasonable question.

I didn't advocate one way or the other. I just said it's very difficult to answer these questions. I worked nine years on a trial that was closed two years later, because it didn't accrue, and that was asking early versus deferred hormonal

therapy questions.

But in non-metastatic castrate-resistant prostate cancer patients, in the high risk group of patients, those that had a very rapid PSA progression following a local therapy, those that progressed while they were getting combined hormonal therapy or radiation therapy, while they were still on the hormonal therapy, patients with high risk disease, high stage, high PSA doubling time -- so we can define them.

I don't think this is the right time to do it, but we sort of have a very good idea. We just need to agree, high risk patients that will progress with castrate-resistant disease. When they developed metastatic disease, the data that we have in various different experiences will support the fact that that's a bad event. That is likely to be associated with survival, with an increased risk of mortality.

So we don't know exactly what the best threshold is. But I think that maybe our objective here today is to agree that this is worthwhile

studying and come up with ways where we can use a progression in the bone -- since we agree that that's of clinical significance, and some of us agree that that may be a surrogate for survival here. I do. Maybe designing trials that would validate that observation, maybe like co-primer endpoints, may not be something we -- we have to start one point.

DR. NING: Right. That's the reason we presented our design 2, early versus delayed trial to demonstrate clinical benefit, depending on the time of progression to initiate the treatment.

DR. WILSON: So I want to turn to Dr. Wozniak, but let me just make one comment. I think there is a difference in endpoints for clinical trials to show something is biologically active and whether or not there is enough clinical meaning to justify approving a drug.

I think this is the very issue the FDA wants us to try to give them some guidance on. The sponsor is going to be coming to them and saying, okay, what is an endpoint that we can use for you

to be convinced that there is meaningful clinical benefit for drug approval. Simply delaying metastatic disease by two months, even with a positive p value, I just know from other trials we have had here, that's just not robust enough for approval. It's very important as a biologic and academic endpoint, but it's just not -- and so I think we need to focus on what best advice can we give the agency in terms of the kind of endpoints for approval.

Dr. Wozniak?

DR. WOZNIAK: I just have a couple comments.

I think it should be time to any metastases, not just bone, because any metastases is fatal. I agree. I know it's going to be bone most of the time. And I don't think we should look at time to symptomatic metastases, because I don't think that's going to be an acceptable endpoint, particularly for patients. They're not going to want to wait for symptomatic. Once they know they have a metastasis, they're going to want treatment. And if they think they get PSA anxiety, they're

going to get metastasis anxiety. That's my opinion.

In terms of the delay, what's important? I don't think we're going to know that until, but we can make somewhat of an educated guess that what we think might be good, because if the time to getting -- once you become castrate-resistant, if the time to getting a bone metastasis is about 30 months -- I guess that's the median time, from what I've heard -- well, maybe six months is a reasonable time. You know, I don't know. That may not be enough. But I think we can make somewhat of an educated guess.

DR. WILSON: Dr. Armstrong?

DR. ARMSTRONG: So sort of looking at the questions that we were asked, it sounds like, listening to the audience, that for the hormone naive patients, probably the only kind of trial you could do would be typical, standard androgen deprivation therapy versus some alternative hormonal therapy. I mean, presumably, maybe SARMS, other drugs that are maybe coming down the pike may

be reasonable to look at in that situation. I know, Mario, you've looked at complete androgen blockade versus just the LHRH agonists, as well. So I don't know if that's still considered something that is a question or whether everybody is getting dual blockade.

But there are presumably alternative hormonal agents that could be studied in that situation, correct?

DR. EISENBERGER: Yes. I think we can talk about several designs and specifics. I'm sure that many of us here can come up -- but one design certain would be patients who are receiving hormonal therapy, which is very common, and their PSA goes up. But it's common. It's essentially a standard approach.

DR. ARMSTRONG: And so you keep tweaking the hormonal therapy as time goes on.

DR. EISENBERGER: It's adding hormonal therapy, and they can add hormonal therapy plus/minus a new compound, for instance, and look for time to metastasis in the high risk group of

patients.

DR. ARMSTRONG: Well, I'm just talking about initially, because it sounds like whether you were high risk or not, if your PSA goes up, it sounds like people are uncomfortable. I mean, these trials looking at delayed androgen deprivation just have not accrued. Nobody wants to do that. So to me, that's a nonstarter.

So if you're going to -- by definition, these patients are going to get some type of hormonal therapy. This would be the situation where you can look at alternative hormonal therapies, for example.

DR. EISENBERGER: Yes. I think that --

DR. ARMSTRONG: But I don't think delayed androgen therapy -- it sounds like that's been tried a bunch of times, and it doesn't work, because nobody accrues patients to the trials.

DR. EISENBERGER: One design would be to get patients who have a very rapid PSA dynamic, very rapid rise in PSA, some other features that we may want to agree, and they get started on hormonal

therapy, without getting into the merits of yes or no. They were started on hormonal therapy. And that subset of patients demonstrates evidence of disease progression, again, with a rapid rise in PSA.

So the standard -- and they're treated with hormonal therapy, just LHRH agonists alone, and then you would, for instance, randomize them between adding a second-line hormonal therapy, whichever a group can agree. Both arms will get it, with or without a new compound, a bone targeted approach, any other.

DR. ARMSTRONG: So I guess my point was there are things that one can do with the hormone naive patients or the patients who are still on initial hormonal therapy that you could look at. But I think doing delayed treatment just is a nonstarter.

Once you have somebody who's on androgen deprivation therapy and they're showing evidence of progression, it seems to me, based on all the discussions today, that if you're going to do a

trial in that setting where patients have non -- I would say, I guess, occult metastatic disease. It's not really non-metastatic disease -- but that you really have to concentrate on the high risk group, because your time to event, particularly if you want to look at survival, is just -- you can't do it in the patients who are lower risk.

It sounds like the one thing that everybody agrees on for high risk is the PSA doubling time. And so it seems like -- and then looking at the graphs, their median survival is about five years, and that's a reasonable group of patients to look at for survival as an event.

Now, I don't know if you go back -- and you guys may know that data, but if you go back and then look at some of their other prognostic factors from diagnosis, such as seminal vesicle invasion, what was their initial PSA, did they have positive margins, what was their T size? What was their Gleason? So you kind of maybe even in the rapid rising PSA group have an even higher risk subgroup so that you could get an event -- the events will

happen more quickly. But I think you do have to have a non-survival event, because, otherwise, these trials are going to take a long time to accrue to.

I would argue that we have to be careful about things like some of the -- like the newer modalities for looking at bone metastases and the same issue that happened with PET scans, which is you pick these up sooner and you'll get sort of a -- not a stage migration. I guess it is a stage migration, but you're going to be picking up disease more quickly. So you have to be very careful about defining what you use to define that progression. But it seems to me that's a good group of patients in terms of looking at new things.

I would say the final thing you have to address, which -- and in respect to the speaker, if you are looking at something new, the whole issue, I think you have to decide whether continuing the same androgen deprivation therapy is going to be what you're going to do or not. And I told you my

feeling, which is based on treating breast cancer, which is if it's not working, it's not going to work and why you continue it.

You guys have to decide that, whether you want to do that, but I think you -- but you have to decide that, whether that's something that you need to continue or not. And I would argue that you might actually be shooting yourselves in the foot if you continue that, because you might actually be using agents in which using them with a hormonal therapy may impact on their efficacy.

DR. EISENBERGER: I agree with a lot of the things that you said, but I just one more thing here.

Over the past two years or so, we've had so much happening in prostate cancer, so many different things. We take an immunotherapy that doesn't delay progression, doesn't change PSA, but it does appear to have a delayed effect on survival.

The treatment choices are many now, and I would imagine that, like with hormonal therapy, it

will vary from treating physician to treating physician, and it will be very difficult to control for that at the time of progression.

For instance, for symptomatic progression, which I would say it's not as likely as it used to occur in the past, partly because they did not have data -- if you use a specific immunotherapy, that is unlikely to delay progression, based on what we know; whereas, policies to use cytotoxic chemotherapy, it may delay progression at that point in time.

So in that, if we cannot -- or another hormonal therapy, a third line, a fourth line hormonal therapy, that may delay progression. Hopefully, we'll see some of that data coming in soon. To control for that will be a nightmare.

So I would say this, again. High risk patients, fast doubling, poor risk, were started on hormone therapy for whatever reason, PSA went up to a certain level and it continues to double, that patient gets started on whatever next standard therapy is, with or without a new treatment, and

time to bone metastasis is a reasonable endpoint.

Let's design this study so we can put the jury out there, use survival or any other additional endpoint that could be of clinical significance, and let's get started. This patient population is out there. There's an unmet need. We need to do the trials. We need to do the best we can.

Therapy, if it changes progression or if it decreases substantially the incidence of bone metastasis, substantially -- we can talk about that -- not two months, not three months, but maybe six months, maybe a year in that group of patients, I would bet here that this is going to make a difference. And that's what I think we need to focus here on today.

DR. ARMSTRONG: I just had two more points. And the first was that I think -- the other point that's been brought up is that the definition of castrate-resistant has not been completely agreed upon, and so do you need a certain testosterone level, do you need evidence. So that needs to be

agreed upon.

Then the final thing that I would suggest is that you need to look not just at overall survival, but disease-specific survival, because if you change the natural -- if some treatment changes the natural history of the disease, you might actually start seeing patients who die of other diseases because they survived their prostate cancer.

So I would just argue that it's not just overall survival, but disease-specific survival needs to be looked at, as well. Thank you.

DR. WILSON: Derek, you had a comment.

DR. RAGHAVAN: Yes, a couple of things to say.

I think what we can do today is paint a broad canvas. And as Mario said, we can't design the trials around this table. So we can make some bold statements to help the FDA and try to move this forward.

So the first bold statement is you have to think completely differently about new versus hormone-resistant disease. The paradigms are

different. For the patient who previously hasn't had hormones, probably the driver is the Messing study in the adjuvant setting. It was published in the New England Journal and then subsequently updated, that showed that early intervention for locally extensive tumors makes a difference to survival. It's a big one. And so that changes the context of whether you delay or don't delay. That's a totally different setting from a patient who is progressing on hormones.

So the first thing I think is we need to divide the two.

The second is there will not be a perfect answer for what is okay for delay of metastasis. I personally think a meaningful endpoint would be a year. I wouldn't argue the point of 11 months or 13 months. I think a year is nice and clean. It allows you to identify a real biological impact.

The downside of setting a year is that you will miss a smaller biological impact, but it's a reasonable point. And so at some point, the FDA is going to have to say how big an impact for anything

do we want to see. Three months is nonsense. Less than three months is even crazier.

The third point I would make is that we've all indicated a consensus that in the patient who's on hormones and has a doubling time of less than three months, irrespective of any other prognostic variable, those patients will die fairly quickly and they have an urgent need.

Then the final point I'd like to make is I really have to take issue with the bold statement, unsupported by data, that it would be unethical to discontinue hormonal therapy. I heard strong advocacy for continuing hormones and I must assume that Dr. Smith has teenage daughters or young daughters of marriageable age, and he's advocating for their protection, because the reality is I've never had diabetes advertised as a good thing. And the fact of the matter is there are no data to indicate that it is unethical or inappropriate to discontinue treatment.

Rather poor studies have been published that suggest that continuous and intermittent androgen

deprivation are equivalent. The definitive study has not yet been reported. And so the absence of data here is not informative. Throughout the country, for a range of reasons, physicians and patients will discontinue hormonal therapy when the patient is in remission, and there are no published data to suggest that in an observed situation, that's a bad thing.

I make the point because this is on the record, and it would be a shame to have all the malpractice attorneys running off and advertising, "If you had hormones discontinued, call 1-800-trial attorney." It's a ridiculous statement, unsupported by data.

DR. WILSON: Dr. Mann?

DR. MANN: Yes. I think what I'd like to also state is that surrogacy is not a matter of how one feels about it. It's, at a minimum, a matter of finding a correlation between, so-called, your surrogate marker and your primary endpoint. And to have adequate power to look at both, you cannot have a study which is powered for disease-free

survival or any other kind of intermediate endpoint, and it has very poor power for overall survival.

So to dissect the patient benefit further, one can look at both of these endpoints. Our DOD-9408 was very recently reported in intermediate risk prostate cancer. It showed both overall survival benefit, as well as disease-specific survival benefit. And the difference in both arms is about 5 percent. And that was an intermediate risk population, about 900 patients in both arms.

So we are talking about a patient population which has already failed hormonal treatment and has underlying disease. I think in this patient population, if you can select a high risk patient population, you should be able to do a study with a reasonable sample size and within a reasonable length of time, because, as I'm sure you know, it's not the sample size itself, it is how many events are happening there and what the difference is between the two study arms.

DR. WILSON: Okay. Thank you.

Dr. Penson?

DR. PENSON: So I'll continue the discussion about outcomes, and I'll say that as a urologic oncologist, I'm sort of with everyone else on this side of the table, which is metastasis is bad. But when I put on my clinical epidemiology hat, I'm sort of with Dr. Wilson that says it may not necessarily be a good endpoint, and didn't we learn anything from the supposed (ph) LT experience, where you have an agent that showed no difference with progression, but showed a survival benefit. And, yes, with a cytotoxic agent, we would expect to see both an advantage for progression and an advantage for survival, but not all of what we're going to see is going to be cytotoxic.

So I end up in the situation where I say -- and maybe I'm sort of playing off both sides -- so you probably need a variety of endpoints.

That brings me to my next point, which is I respectfully disagree with Dr. Mann. In this setting of the M0 CRPC, you really can do that

trial number 2 design, early versus late treatment of a new agent, and perhaps the trigger is that metastatic event. So you get a bony mets, and then you get unblended, and you go on to delay treatment if you so desire it, and that may work. I also think it's very important to get patient-reported outcomes.

The last point I want to throw out there for thought is something that -- we've talked about this a little bit already, about ADT and hormonally naive patients. I think you're hearing here that in some of these patients which are hormonally naïve that have rapidly rising PSA, they really need ADT. They need some sort of treatment.

Well, I'm concerned that if we restrict these trials in the M0 CRPC patient only to high risk patients, that once an agent gets approved, we're going to have a lot of off-label use in low risk patients.

So I would argue that as we think about trial design, while we want to focus and enrich studies with high risk patients, I think you want

to think about including some low risk patients and maybe stratifying, so in the end you can say it did work in the high risk patients, and the low risk patients we actually have a true absence of evidence and maybe it shouldn't be used in that off-label setting.

DR. WILSON: Dr. Garnick?

DR. GARNICK: Just a few additional comments. A lot has been said. I think from the regulatory perspective, it's very important for the agency to appreciate that patients who have a rising PSA following definitive therapy, whether it be radiation or a radical prostatectomy, are a very, very heterogeneous patient population.

There's been a lot of discussion about the rapid PSA doubling time. You can have a patient that has PT3B disease whose PSA comes up within several months following radical prostatectomy that is a very, very high risk patient. You can also have patients who have had a prostatectomy, they have a focal margin positive, who end up having a PSA rise that comes up four to five years post-

prostatectomy that has a very, very different biological outcome.

So I think in any study design, it will be very important to capture this sort of clinical situation that the patients were in before they ended up having the rising PSA.

The second point, I think it's very important for us to -- in the light of what Dr. Smith discussed, it's very important to have a cardiovascular risk profile for these patients. We're learning that ADT does prolong the QTC and, in the past, if a patient or an elderly patient dropped dead who had prostate cancer, was on hormonal therapy, you really didn't give it a second thought that it was related to the hormonal therapy, but rather related to cardiovascular preexisting situations.

So I would really urge that some sort of cohesive and homogenous risk assessment of the patient's cardiovascular metabolic status get captured before any individual study. And then in terms of attribution of causes of death, there is a

huge disparity in terms of attributing whether patients die of prostate cancer, complications of therapy or complications of systemic therapy. And I think it behooves us to try to try to address that prospectively in trying to actually prospectively identify issues so the cause of death is not ambiguous. And so in terms of quality of life issues, we have more substantive data after these studies are designed and completed.

DR. WILSON: Okay. Thank you.

Dr. Logan?

DR. LOGAN: I just wanted to make a couple comments about some of the endpoints that have been talked about. There was some discussion about time to symptomatic metastasis. It seems to me that this has more direct clinical meaning than time to metastasis itself. But in order to implement it, you need to do something similar to what you do with survival. The patients are not going to wait for intervention until they get symptomatic metastasis. So this requires continued follow-up in those patients and allowing for intervention

after the initial metastasis develops.

So it requires longer-term follow-up, similar to what's done for survival, except it's a little more complicated.

In terms of defining a magnitude of benefit in terms of something like time to metastasis or metastasis-free survival as a potential surrogate endpoint, it seems to me that a lot of this hinges on the duration of time from metastasis to death.

If that's a long duration of time, then you would need a longer potential benefit in time to metastasis in order to better predict for a survival benefit. It's also important to remember that what's considered a clinical benefit will depend on the toxicity of the intervention.

There was a mention about potentially a high incidence of the competing risk of death without metastasis, particularly in these older patients. It seems to me that rather than time to metastasis, it would be better to use metastasis-free survival, because it includes the potential impact of the interventions on toxicities, which would then be

reflected in non-metastasis mortality. And that may better correlate with overall survival, as well.

Then just one final comment on the early versus late design, design 2, where the treatment has been approved for -- is an approved treatment at metastasis, here, you can't use metastasis-free survival. You need to use overall survival or perhaps time to symptomatic metastasis because of the early/late design.

DR. WILSON: Okay. Thank you.

Dr. Zones?

DR. ZONES: I have a couple of comments. One about Dr. Smith's claim that discontinuation of ADT for this group would be considered unethical.

I'm remembering that almost the entire medical establishment made this claim that it would be unethical, before the Women's Health Initiative, to deprive post-menopausal women of hormone replacement therapy by randomizing them into a placebo group, and we know what happened there.

I support Dr. Wilson's comment that we need

to preserve overall survival and quality of life as our major endpoints. That doesn't mean that there can't be other endpoints that are more intermediate.

But I'm thinking about tamoxifen, which didn't have survival as an endpoint. The endpoint was reduction in risk of recurrent breast cancer in women who had been treated for early breast cancer. And they ended the -- they discontinued the trial after about six or seven years, but it just before there was about to be a crossover where the women in the tamoxifen group were going to have higher mortality than the women in the placebo group because of the effects of tamoxifen.

So I think it's important to keep overall survival as our primary endpoint.

DR. EISENBERGER: Just a quick comment. I think all you said is very important. There's no question about we need to know a few more things. But the reality here is that patients get treated with hormonal therapy. I would actually just extend a little bit on what Matt Smith said. It's

not that it's not perhaps unethical. I don't know what I would use there. But it's actually the facts of life, standard of care.

So for us to do clinical trials and go against what most of the people would consider a standard of care, I think we're asking for failure. We're now going to be asking patients, and doctors, particularly, who standardly receive hormonal therapy, to stop it in order to do the trial, I think we're making the bar even higher, more difficult.

Not to say that your questions don't have any scientific merit, they do. But we're trying to focus again on a group of men who have high risk disease, who were placed on hormone therapy because it was perceived that they have a high risk disease, and now they have a biochemical relapsed disease with low levels of testosterone, and we can define that, and their PSA is going up rapidly.

So, yes, I don't know whether stopping hormone therapy or not is a benefit, but it's so unlikely that this will be accepted in a clinical

trials community, that we're asking for failure.

I also think that to ask the question on can we do something in that patient population to delay the onset of metastatic disease is a very pertinent clinical question, even though it's different than yours.

We do have a real opportunity to do here. And, again, this is an unmet need. This is a huge patient population. We do have the compounds and we have the opportunity to do it. So I think we should focus on that and do the clinical trials on these patients and define endpoints as we design our trials.

DR. WILSON: Okay. Thank you.

Dr. Loehrer?

DR. LOEHRER: Just a couple of brief comments. I think from the unmet need point of view that was brought up earlier, it seems to me that the best unmet need are the castrate-resistant prostate cancer. The hormone naive patients, there's a lot of treatment out there for them right now and there's a lot of options, and I think

they're going to do okay. And then that sample size is going to be so huge to show a small difference. And limited resources, I think the unmet need is what particularly that side of the room has defined as high risk patients with rapidly doubling PSA, at least from my point.

The other point, to Marc's point, I think, again, there are nice assays -- there are nice -- I'm not sure of the right word, but geriatric assays that are out there. And I think that we ought to incorporate some of those as opposed to just using performance status, as what we would tend to do. We really ought to assess strongly these patients and look into other outcomes.

Then a final point has to do with this tie to metastases or metastases-free survival, which is fine. I tend to think overall survival is better. What has been missed in this conversation is that, particularly in patients who are on hormonal therapy for a long period of time, the first skeletal event may not be from cancer. A positive

bone scan may be from some other reason, including benign fractures from osteoporosis. Unless we biopsy all those, it'll be difficult. If you happen to roll over badly in bed and you have osteoporosis, the bone scan may be positive, incredibly so if you used a fluoride scan.

So that time to metastases is going to be a little blurrier. I think overall survival is clearly where we want to go.

DR. WILSON: Okay. Thank you.

Dr. Sekeres?

DR. SEKERES: Thank you, Dr. Wilson.

This has been a learning experience for me, also, to hear all of the opinions of the expert GU oncologists in the room.

It sounds like, whether I understand it or like it or not, the standard of care has been for patients who are perceived as being high risk and hormone naive, to start hormones in them, whether or not the prospective study directly supports that patient population. And that's okay. I mean, we do this all the time in oncology. We don't have

great data for sending our AML patients who have poor risk set of genetics to transplant and for CR.

We've got a bunch of phase 2 studies at single institutions and we have some retrospective studies supporting it, but we got what we got and that's the practice and we're never going to have a randomized study to look at that.

Given that, I think that the second trial design is just simply never going to happen. And I agree with everything that's been said around the table about that. I don't think we should beat ourselves over the head with it.

In defining a higher risk population to look at and talking about time to first metastasis, or I liked event-free survival, that incorporates not only time to metastasis, but also bone metastases, any metastases, and overall survival -- and with apologies to Dr. Smith's daughters, cardiovascular morbidity and anything else that may occur, because in a trial design that's going to look at this question, it's going to require so many patients, we are going to see some folks who have heart

attacks that are probably tied to hormonal therapy.

Given that we're talking about an interim endpoint, though, I want to reflect back on what Dr. Wilson said about half an hour ago. I'm very, very worried that we may be sending the company to a premature death at our own hands a few years from now when they come to us with a moderate improvement in an interim marker, but no overall survival advantage. I really do think we have to push for overall survival, or at the very least look at event-free survival with a patient-reported outcome as a dual endpoint.

DR. KLUETZ: Can I make one clarification real quick?

It is that the trial design number 2, the early versus delayed, was not with respect to early versus delayed hormonal therapy -- I just want to make sure everyone recognizes that -- but rather a trial designed to consider drugs that are currently approved in the metastatic setting -- there's four of them -- to use -- or if another drug becomes approved in the metastatic setting -- to use that

in this space versus to use it in its approved setting. Are we just moving the exact same response and duration earlier with an identical overall clinical benefit?

So that was just a clarification.

DR. WILSON: Actually, that's a very good one, because I think that's a little bit different than what a lot of people thought you meant by that.

Dr. Kelly?

DR. KELLY: Thank you.

Just a couple clarifications on endpoints. And we talk about metastatic -- development of bony metastasis is symptomatic, you have to be careful. That's a slippery slope, because the major symptoms patients develop with this disease is fatigue, not bony pain. So you have to be very careful how you actually define symptomatic metastatic disease in that.

The other one is using survival as an endpoint. If you use these drug acts or whatever very early, we have so many new treatments down the

line, and there's no consistency in what order we use them. I have no idea how to sort out the impact of these additional treatments down the line. So I'm very concerned that survival would not be a viable endpoint.

So we have to struggle with that a little bit, because we have a lot of riches out there, and I'm not quite sure that we'll be able to tease all that out.

DR. PAZDUR: We see this in every disease, and this is a common complaint or comment that is made, drugs that may come around. Remember, we have a randomized study here. So one would have to assume that in a randomized study, new therapies are allocated in a random fashion to each arm. And remember, we're approving a drug in the context of existing therapies. So these are existing therapies that are there.

So we see this comment frequently. But we really don't put a lot of weight in it in the sense that here, again, as new therapies come out, if you have a randomized study, they're randomly being

allocated to each of these arms in a random fashion. So unless there is some sort of bias that would exist in the subsequent treatment of patients, that might come up and might be able look at.

But we're really approving a drug in the context of existing therapies. And I think the CTEP people recently wrote an article on looking at survival as a preferred endpoint in many disease settings, and that's a point that they make.

DR. KELLY: Rick, the point I'm trying to make is just that we're dealing with a very heterogeneous population. And there are treatments out there that are approved that may be better in some of those populations than the others. Unfortunately, we don't know which groups are best to do it.

So you have a lot of variables there, and I'm just saying there's a lot of variables to consider, and to put your own legs in survival, it may be concerning.

DR. KLUETZ: I think we totally agree that

there's heterogeneity in the population. And we tried to bring up, and I think everyone has brought population, that enriching this population even after hormones is critical to find that population that may benefit; not only sort of ethically to find the patient population that would benefit, but if you're a drug company, to get their endpoints in a timely fashion that you need to get and to have overall survival as a realistic endpoint, which I think, given the data that I've seen, could be a realistic endpoint.

DR. WILSON: Dr. Garnick?

DR. GARNICK: I'd just like to raise the issue again of continuation or not continuation of hormonal therapy. I know there's been a lot of discussion on the use of terms of unethical and stuff like that.

To me, it's this very, very studiable endpoint. Many patients, if they've been on hormonal therapy for several years, are unlikely to ever develop normal testosterone levels. So if you continued to monitor testosterone in addition to

the novel agent, to me, that would be a very, very studiable and a very important consideration for moving forward.

There are some patients that are going to recover. Some of the study designs could actually include reinducing those patients to getting a castrate level of testosterone, depending upon what the additional agent is, whether it affects testosterone.

So to me, it's a -- and I understand there's a lot of emotional discussion, but in terms of the data to support it one way or the other, to me, it's a very, very important question and may actually have some issues related to improvement on quality of life if you discontinue it, and the patients are unable to regain that testosterone.

But, again, I don't have the answer. I'm just saying it to be a consideration for the late versus early interventions.

DR. RAGHAVAN: And it may be worth just adding, Marc, that -- and I agree with everything you said. My point was that it's ethical to study

it as opposed to unethical to study it.

But keep in mind there have been datasets that have indicated that you can measure adrenal androgen function. It's an easy stimulus to measure of prostate growth. So in the patient with no measurable testosterone, but very high levels of DHEA and DHEAS, that may be informative.

Now, whether you actually want to build that into the study or create a study that has a serum bank that can be interrogated at a later time can be decided later on. But just keep in mind that it isn't only testosterone that drives prostate cancer.

DR. WILSON: Dr. Wozniak?

DR. WOZNIAK: I was thinking about the overall survival endpoint. I think it is the ultimate endpoint, but I think it depends upon the disease you're treating and, also, where you are in that disease. It might be the right endpoint for metastatic lung cancer, which is what I have to deal with, but in prostate cancer patients who tend to live a long time, it may not be the right

endpoint. But it all depends on where you are. If there are failed multiple treatments, then overall survival may mean more. But when they live a long time and there are multiple treatments available, it' going to be hard to go for that overall survival endpoint.

DR. WILSON: So I just want to say, once more, that if you are treating someone and your trial hasn't been going for long enough to have an overall survival advantage or doesn't have one, you want to make sure that whatever surrogate you have chosen either is improving that person's quality of life or you are absolutely convinced that down the line, four or five years later, way beyond your trial, that it is going to improve overall survival.

So I guess, once again, I just think that we have to make sure that we're really helping folks and that we're not basically getting a radiographic finding.

Dr. Loehrer?

DR. LOEHRER: I just had a quick question

for you guys, the prostate people there.

Circulating tumor cells, are there other measurements of things that we should be -- can we look at besides the typical things that we're doing?

DR. MANN: I think Dr. Scher probably will be the best person to answer.

DR. SCHER: I think the trials have to be embedded, designed in such a way that we can answer these questions. You talk about a serum bank, you talk about imaging. That's the only way we're going to understand what the significance of any change that we see post-treatment ultimately means.

If you think about the four products that have shown a survival benefit, they're all very different. So I'm not sure how you would practically implement a delay trial in a patient population that's getting a biologic, versus one that's getting a hormonal therapy, versus one that's a cytotoxic. You can't lump them all together. And if the triggers -- if you think about reimbursements, and wearing sponsor's hat,

they want to get reimbursed in the non-metastatic castrate setting, what's the trial they need to do to do that? If the trigger comes too early, they're not going to see a survival difference.

So does that mean it doesn't work or it did?

So just trying to get to a little bit of the realities that we face every day. How would you actually demonstrate that?

The second thing, circulating tumor cells is undergoing a prospective, formal regulatory path trying to see if it may add to an outcome measure post-treatment that can associate with survival. It's embedded in the Cougar 301 trial that showed a survival benefit. It's in the MedNovation (ph) trial, it's in the TAK-700 trial. So there are several studies that are now including that biomarker.

The detection rate in the rising PSA castrate setting is highly variable, with the existing clear technology, but there are other technologies that are currently undergoing the analytical validation process and, hopefully,

they'll be cleared to the point where they, too, can be incorporated in the studies.

But I think the metric here is to create the framework where patients are followed at regular intervals, the imaging is appropriately interpreted, so that you can ask the question, does it associate with subsequent development of symptoms, does it associate with survival, and then we won't have to go in circles.

But if we keep saying -- if we stop following patients and don't consider subsequent therapy -- and I just want to raise one question.

Yes, random assignment post-treatment can ideally balance, but those trials would end up being much, much larger than they're currently designed for, and we don't know the issue of cross-resistance. So you can't assume that therapy A, that prolonged survival benefit, after therapy B, will be the same as if it's given after therapy C. Those are independent questions.

So I wouldn't throw that out quite that easily, because, again, I think it would have to be

leading to a much larger initial study in order to make sure that there's balanced distribution in the groups.

DR. WILSON: Okay. Thank you.

Dr. Freedman?

DR. FREEDMAN: Since I'm the only gynecologist here, I think I might as well end up with a question, but I've been listening very carefully to what's been said. And, clearly, the urology consultants here have identified risk populations to be treated.

But I think a key thing in developing a clinical trial is to have an idea for the potential risk-benefit in that population that you're going to treat. And, as has been mentioned, the drugs that's going to be used here -- and it's been brought up by Dr. Garnick, I believe, in some previous discussion -- they have the potential to cause problems.

So the question that I have to ask you, these are patients that are probably going to have to be treated over a long period of time, maybe

years. I'm not sure, but that's a question for you to address.

Do we know enough about the effects of these drugs that are currently available, they're commercially available, although they may not be approved, in terms of their effects in relation to the duration of treatment, the dosing, and, at the time, to develop the problems that are associated with those drugs?

I think the benefit side we can understand; it is clearer. But the issue of being able to design a trial that incorporates that -- because ultimately you're going to have make a decision on risk-benefit. You can project for the benefit knowing the history of the disease, but can you give a projection for the risks when you -- in relation to the duration of treatment in these factors. How much do we know?

DR. GARNICK: I don't think we know very much. I mean, I think the agency is going to be asked to potentially identify chronic use of agents that are approved in the metastatic setting, in a

non-metastatic setting in which the duration of therapy may be very different from which the agent was actually approved for.

For hormonal therapy, we sort of thought that LHRH analogs were devoid of cardiovascular risk factors when those studies were first presented to the FDA and gained approval, when Leuprolide was compared to DES, with decades of information, and now we know it's got a completely novel and not well studied set of metabolic abnormalities that were not appreciated when those agents were first used.

I can imagine the same things happening with drugs such abiraterone or other agents that are currently approved in which the duration of therapy in the non-metastatic setting is going to potentially be much longer than the duration of therapy that was used in the metastatic setting when the side effect profile has been better defined.

DR. FREEDMAN: This is going to be important when you recruit the subjects to these trials.

They want to know -- you've told them about the potential benefit, but they want to know the potential risks. And how are you going to be able to define this risk in a clear manner, clear enough manner for them to be able to make a decision whether they want to participate. So they will want to know about frequencies and severities. It's an important issue to understand.

DR. GARNICK: I think the duration and the dosing schedule, especially the schedule of administration, will be very, very important whether intervening in the early design versus the delay design.

DR. NING: Well, I guess that treatment initiation started at non-metastatic CRPC setting, may have longer exposure to the drug. So that would be balanced if you see more clinical benefit, such as prolongation in survival.

DR. KLUETZ: I also think it has everything to do with what agent you're studying, because some agents, you're not going to use cabazitaxel for 50 months. It depends on if it's a cytotoxic or

hormonal. We now have immunotherapies. It's going to be very specific to the therapy being used and whether you're going to stop it upon progression.

DR. GARNICK: But, for example, the abiraterone could potentially be used chronically, if you're going to look at that in the non-metastatic setting.

DR. NING: Right. I say to that we definitely have kind of a difference between cytotoxic and a non-cytotoxic agent. I doubt that a physician would initiate chemotherapy in non-metastatic setting, and we have to follow our common sense.

DR. MANN: I think the other issue is many of the drugs, for example, abiraterone, which were initially approved in metastatic disease setting -- and it is given with prednisone. So these patients, they do not really reflect the long-term toxicities of any treatment. When you take the same drug into the adjuvant setting, should you be giving them -- for example, if you are using it or trying to add it to androgen

deprivation therapy with radiation early on, again, you're going to be giving prednisone for like two years.

So I think the toxicity or the adverse event profile, it does change, because it's not only the immediate toxicity. Many of the toxicities are manifested late. For the first 10 years of tamoxifen, nobody knew about endometrial cancers, and there are examples in oncology.

The other point I'd like to make is, overall, trial is one thing. The other -- if you have a clinical benefit endpoint, some kind of asymptomatic progression or anything else, the issue there is censoring deaths which are being labeled as other cause, but they may be related to the drug or the disease. That is the big issue I have for that.

DR. WILSON: Okay. We're actually coming up on 5:00. And I think we've had a very good discussion.

May I ask FDA if they have any pressing questions?

DR. KLUETZ: I would just make one last comment that there's been a lot of talk about surrogates with respect to -- we talked a little bit about circulating tumor cells, you could talk about PSA, and I think you can talk about asymptomatic metastatic disease as a surrogate for overall survival.

But as Dr. Scher notes, there is really no way to find out whether these are true surrogates without some form of what we believe to be clinical benefit in the trial. And so that's important to remember if we wish to establish any of these surrogates.

DR. WILSON: Does anyone on the panel have any final closing comments?

[No response.]

Adjournment

DR. WILSON: Okay. With that, let me thank the panel, let me thank the speakers. And we are now adjourned. Thank you.

(Whereupon, at 4:57 p.m., the afternoon session was adjourned.)