TRANSCRIPT

Castrate-Metastatic Prostate Cancer:
Therapeutic Considerations for Advanced Disease

Dr. Robert Dreicer

March 25, 2010

Slide 1: Welcome

Operator:

Hello, everyone, and welcome to *Castrate-Metastatic Prostate Cancer: Therapeutic Considerations for Advanced Disease*, a free continuing education webcast. It is my pleasure to introduce your moderator, Dr. Sherri Kramer:

Dr. Sherri Kramer:

Hello, my name is Dr. Sherri Kramer, director of medical affairs at Robert Michael Educational Institute, and I will be your moderator for today's webcast. I would like to welcome you to *Castrate-Metastatic Prostate Cancer: Therapeutic Considerations for Advanced Disease.* This is a continuing education activity accredited for physicians, pharmacists, and registered nurses. The activity is jointly sponsored by Robert Michael Educational Institute and Postgraduate Institute for Medicine and is supported by educational grants from sanofi-aventis and Genentech.

The webcast will last for 1 hour with approximately 40 minutes for our presentation and 15 minutes at the end for questions and answers. At the conclusion of the activity, I will provide instructions for receiving CME credit.

Slide 2: Castrate-Metastatic Prostate Cancer

Without further delay, it is my pleasure to introduce our speaker, Dr. Robert Dreicer. Dr. Dreicer is chairman of the Department of Solid Tumor Oncology at Taussig Cancer Institute and professor of medicine at Cleveland Clinic Lerner College of Medicine in Cleveland, Ohio.

Dr. Dreicer, please begin.

Dr. Robert Dreicer:

Thank you. Appreciate those of you who have joined us either this morning or this afternoon. What I want to try to do for you over the next 30 or 40 minutes is talk about a disease that is in relatively rapid evolution. Of note, even in the month or 6 weeks in time since I made these slides, there have been changes in the medical literature and presented at national meetings that have actually changed

some of the slides that I've utilized. I think that's actually a very important piece of perspective.

For those of us who are a bit older, prostate cancer management for many years basically was relatively static, the role of hormonal therapy established more than 6 decades ago. But in the last couple of years and going forward over the next couple of years, I think we're going to see some very rapid developments in the management of this disease.

Slide 3: Disclosure of Conflicts of Interest

So, my conflicts of interest are listed on this slide for you to review.

Slide 4: Learning Objectives

Here are the learning objectives for today's presentation.

Slide 5: Clinical States in Prostate Cancer

So looking at this first slide, a number of years ago, a friend and colleague of mine, Howard Scher, who runs the geo-medical oncology program at Memorial Sloan-Kettering, presented a manuscript in which he described the clinical states model in prostate cancer. The slide before you is a modification of that initial presentation. I think this particular slide depicts not only a way for clinicians to think about disease management, but increasingly as clinical investigators and as we begin to think about trying to manage prostate cancer increasingly as a chronic disease—meaning those patients who've undergone definitive local therapy for organ-confined or locally advanced disease who have not been cured, those patients who have PSA failure post-definitive local therapy and then go on to develop systemic manifestations of disease—this is a very important way to think about the disease. Because as we develop additional treatment methodologies, where we apply them, when we apply them, in what sequence we apply them are going to be increasingly important. We'll come and touch back on this as we go through the presentation.

Slide 6: Castrate-Metastatic: Yes

Over the last year or two, increasingly those of you who follow the prostate cancer literature will find that the nomenclature to define the state of disease, once patients have progression with castrate levels of testosterone, has evolved. I'm going to try to give you a little bit of background to try to at least give a sense of why this is actually happening.

The title of the slide: castrate-metastatic prostate cancer, yes, hormone refractory/androgen independent, no. Again, remember from a historical paradigm, what we know is is that in the era prior to PSA, patients typically with advanced disease presented with clinical evidence of metastases. They received hormonal therapy, initially of course by orchiectomy or with estrogens. We evolved to using LHRH agonist therapy as well, and eventually patients became symptomatic after a period of time—typically 18 to 36 months of response to hormonal therapy. They were then felt to be *refractory* to hormonal therapy. So the definition of patients who are castrated, castrate levels of testosterone, has been, in a sense, somewhat arbitrarily picked as having a serum

testosterone less than 50 nanograms per deciliter. So at time of disease progression, folks felt initially that they could stop hormonal therapy. Over time, there was an evolution in the community that takes care of this disease to believe that there was a rationale to maintain low levels of testosterone, even in the face of progression.

Slide 7: Hormone Refractory: No

What's changed over time is an understanding that the disease process is that we now have better drugs that achieve levels of testosterone that were not seen before. So how do we know that these terms are probably misnomers?

Well, we know that there are patients who clearly respond to what has been termed secondary hormonal therapy. So the use of antiandrogens in patients who were treated with monotherapy—I mean, bilateral orch or LHRH agonist therapy—some patients responded to the initiation of a drug like bicalutamide or ketoconazole, so clearly those patients weren't *refractory* to hormonal therapy because they demonstrated a secondary response.

Slide 8: Androgen Receptor as a Target

Other evidence, we know that increasingly androgen receptor signaling—and again the androgen receptor is sort of the Holy Grail of the disease—that's where the target of this disease in terms of therapeutics needs to be concentrated.

Slide 9: Androgen Receptor Signaling is Key

We know that AR signaling continues despite very low levels of serum testosterone, and that increasingly as we develop means to lower serum testosterone to levels far lower than we've seen before, but more importantly, begin to try to deal with intracellular levels of testosterone and its conversion product to dihydrotestosterone. There is increasing evidence that the ability to make that change demonstrates the ability to continue to get additional responses.

Slide 10: Therapeutic Considerations

Let's move forward just a little bit, coming back to the clinical states model, and talking about from a clinical perspective some of the issues that we have to contend with as we manage patients.

Slide 11: Clinical States in Prostate Cancer

In the green, you see a box that's listed as metastatic castrate asymptomatic. So this is the kind of patient who clinically may have been known for a long time to have biochemical failure, may have received androgen deprivation therapy for PSA-only disease, or in fact may have presented–increasingly rare today–with metastatic disease up front, received hormonal therapy. Now because PSA is followed so closely, a patient with castrate levels of testosterone with a rising PSA who is without symptoms would fall into this category. There are a fair amount of these kinds of patients, and the harder we look for them—meaning that if you look at a patient with slow PSA progression

who's been on hormonal therapy—you will increasingly find patients who have very low levels of clinical disease or radiographic disease, maybe a couple of spots on bone scan or small nodal disease. Historically, this patient population has become enriched because of the use of PSA.

Slide 12: Phase III Docetaxel Studies in CMPC

So what do we know about what the standard of care in 2010 is for the management of patients who have metastatic prostate cancer, whose disease has progressed despite hormonal therapy? That leads us to a discussion of what a standard of care is, and that's docetaxel-based chemotherapy.

In 2004, these two large randomized trials were presented and ultimately changed what we thought about in terms of a disease that for many years—and again, there may be many of you who are relatively young and don't remember the era of the 80s and the early 90s where chemotherapy for advanced prostate cancer was used occasionally. It was typically given to patients who were pretty advanced in their disease. These were gentlemen who were really not in the best shape, and, frankly, chemotherapy was relatively toxic and didn't really buy much for the patient in terms of either palliative benefit or certainly some evidence that we were meaningfully altering the disease. So what was so important about these two randomized trials is that for the first time with advanced prostate cancer, a chemotherapeutic seemed to change the natural history.

Slide 13: Overall Survival: SWOG 9916

So the first—this is the survival curve from the Southwest Oncology Group randomized trial, and what you see there is an improvement in survival of a couple of months. I point out that the hazard ratio of 0.8, meaning a 20% reduction in death in those patients who received docetaxel plus, in this study, estramustine, compared to the gold standard of mitoxantrone and prednisone.

Slide 14: Overall Survival: TAX 327

The TAX 327 trial, which was an industry-sponsored randomized trial, had 3 arms: docetaxel either given weekly or every 3 weeks, compared to mitoxantrone and prednisone. Again, here there was about a 2.5-month improvement in survival in those patients who received docetaxel given every 3 weeks compared to the patients who received mitoxantrone. It's on the basis of this study that docetaxel was approved and became a standard of care.

Slide 15: Docetaxel-Based Therapy

One of the things that we've learned over time about docetaxel is it's actually relatively well tolerated, and patients have a relatively high likelihood of responding both clinically—meaning having improvement in symptoms, decrease in bone pain, improvement in appetite if they've lost weight, weight regained—and then decrease in the requirements for pain medication.

Now, one of the major issues about docetaxel is not so much whether or not it works—it clearly works. But what is the optimal time to administer chemotherapy to a patient who has progressive prostate cancer? There have been numerous re-evaluations of the docetaxel data, looking at trying to

correlate whether or not there are other parameters, such as PSA changes, pain improvement, et cetera, that might be able to give us some insight as to when optimal docetaxel administration—when the trigger should be pulled.

Slide 16: Relationship of PSA to Survival

In many of these reviews—and one is listed here that was published in *Clinical Cancer Research* a couple of years ago—none of the sort of easily available endpoints, either PSA or pain response, can really be a surrogate marker for survival. We know that patients who have response to therapy as manifested by decline in PSA or improvement in pain clearly seem to do better. But unfortunately, it is not a surrogate for survival.

Slide 17: Management of Asymptomatic CMPC

The other issue is ultimately when you treat patients who have no disease-related symptoms and have metastatic prostate cancer and you're thinking about the use of docetaxel, one of the issues that I've always sort of thought about clinically is what the goal of therapy is. So when you sit with a patient who has metastatic process cancer, who's asymptomatic, there's this sort of concern on the patient and your perspective of trying to utilize a therapy that may improve survival and improve outcome.

So the question about optimal timing, if I give this therapy now and the patient is entirely asymptomatic, I will likely be able to deliver the therapy effectively, there's no question there. But what happens if I wait until the patient has mild or minimal symptoms? Will I get the same kind of benefit?

Suffice it to say that as we've looked at TAX 327 and the SWOG trial, there's no way to tease out whether or not early versus later therapy is more optimal. We know that patients who have more advanced disease tend to do less well, but they still respond to therapy. So it's not a matter of timing in terms of getting optimal benefit.

One of the things that I use clinically is that if I treat a patient who is without disease-related symptoms, the only symptoms in a sense that I will create is the ultimate side effects of the drug. Meaning, I'm now telling the patient our goal of therapy is to try to provide some ability to improve your survival. But you don't feel badly now, so I'm clearly not going to make you feel better, there's going to be side effects.

But when I take patients who have mild or even moderate symptoms, they get dual benefit. They have the potential for a survival benefit, but they also will clearly almost always feel better. Pain gets better, energy level gets better—and this is a very active drug in this disease. It is not uncommon for a patient to get one cycle of docetaxel-based therapy, and as they come back to see you for consideration of their next cycle, they already feel better. So the ability then to deliver the optimal amount of therapy that you are planning is a lot easier in a patient who has already seen the benefit. It's not just that they see a PSA decline—and I will point out that one of the interesting issues that people need to be aware about in docetaxel-based therapy is a flare phenomenon.

About 4 or 5 years ago, there were sort of scattered reports that patients, who after two or three or four cycles of docetaxel, had a striking increase in PSA. There were some physicians who were using PSA as a parameter to delivery therapy and who backed off. So the classic call that I may get occasionally from physicians in practice is, "I have this patient with castrate-metastatic disease, he was mildly symptomatic, he lost a few pounds and he was using opioids, and I gave him docetaxel-prednisone every 3 weeks, and he's done two cycles of therapy, he's coming back for consideration of cycle 3, but his PSA went from 79 to 120 and I don't know what to do. I think I should stop therapy and do something else." The first question I typically ask is, "How did the patient feel?" And invariably the answer is, "Oh, the patient feels great, feels much better than he did before." So we know that there is a PSA flare phenomenon and that experienced clinicians need to look and talk to their patients because frequently you know that the patient is getting better, the patient is telling you he's getting better, and therefore you have to recognize that, in those instances, you will see PSA decline a bit later.

So again, we don't know the optimal time of administration of docetaxel-based therapy is. It's been my clinical practice to put people on clinical trials who were asymptomatic, when they're interested in being aggressive. But I think that all patients in this clinical setting should at least have a discussion about what optimal therapies are out there. Many patients who are entirely asymptomatic represent optimal patients in whom to do either secondary hormonal maneuvers or to enroll in clinical trials. That's a reasonable segue for what we're going to talk about in just a couple of minutes.

Slide 18: Emerging Therapeutics

Let's move on a little bit, and now let's start talking about where things might be going over the next couple of years. Here is a list of some selected emerging therapeutics in patients with castrate-metastatic prostate cancer. We're going to go through some of these in a little bit more detail, and I'll try to at least touch on most of them.

You see them somewhat delineated based on mechanism. The first group, androgen receptor–targeted therapies, compounds that are lyase inhibitors—and the lead compound in class is a compound called abiraterone. You'll notice that on the right-hand side of the slide I've indicated where the trials in terms of phase III trials are. Actually interestingly enough, abiraterone, which is a lyase inhibitor—again, we'll come back and talk about it in more detail—has already been in two phase III trials. The second trial, which I'll touch on, has already just recently completed accrual, suggesting in the broad community there's lots of interest in these compounds.

MDV3100 is a second-generation antiandrogen, and again, we'll touch on this in a bit.

From the immunomodulatory approach, many of you have followed the Provenge® story, that this vaccine is entitled sipuleucel-T. Again, we're going to talk about this in just a bit.

A compound that we're not going to really spend too much time on today, lenalidomide, is an agent that's already FDA-approved in myeloma and myelodysplastic syndrome. It's a very interesting

compound, it's an IMiD, which has immunomodulatory activity and is currently in a randomized trial with docetaxel in patients with advanced disease.

I referred in my opening remarks about rapid development. Cabazitaxel is a second-generation taxane. I'm going to show you a couple of slides—this is a compound that was not really well recognized in the broad GU community up until very recently. I'm going to show you some, I think, intriguing and exciting data that was presented just within the last couple of weeks at the ASCO SUO ASTRO GU symposium in San Francisco.

Many of you are very well aware of the compounds of bevacizumab and sunitinib, and there are randomized trials in this setting. Again, within the last week or two, we've had some data about bevacizumab, and I'll touch on that.

An area that we don't really have too much time to talk about today: bone-targeted therapeutics, compounds such as the rank ligand inhibitor denosumab and an endothelin A inhibitor, ZD4054—or the name zibotentan.

Slide 19: Abiraterone

So let's move forward and start talking about a couple of classes of drugs that I am hopeful that, within a relatively short period of time, we're not going to be talking about from the context of investigational therapy but agents that we may be able to all use in our clinical practice.

Abiraterone acetate is an inhibitor of the CYP 17 dual enzyme complex, and that's principally responsible for androgen synthesis.

Slide 20: Abiraterone and the Steroid Pathway

On this slide, I've abbreviated a bit the cholesterol breakdown pathway to testosterone and di-testosterone. You can see in red where both ketoconazole and abiraterone seem to impact. One can think about ketoconazole as a drug that is a microcosm in class. It does some of these same things, and those of us who've used ketoconazole over the years recognize that there are a subset of patients who clearly have a response to this agent. There's always been a little bit of concern about the toxicity associated with it.

Abiraterone impacts in this pathway, but it is a dramatically more active agent that basically changes the breakdown product and decreases testosterone and subsequent conversion to dihydrotestosterone.

Slide 21: Phase II Trials of Abiraterone

What I'm going to show you now is just a sampling of the data that's in the literature. Some of these are now published trials, many of them are still in abstract form.

Basically what this is is a series of mostly phase I and phase II trials looking at abiraterone, which is

an oral agent tested in patients who have castrate-progressive disease—in some instances in those who have not received chemotherapy and, in other settings, in those patients who have had docetaxel and then develop progressive disease. Even in some patients who were treated with ketoconazole previously.

I think what you can see, again on a very high level—and these are relatively small numbers, these are phase II trials—that there was unequivocal evidence of both a PSA response as well as an objective response. Those patients who had soft tissue nodal disease with measurable disease responses had improvement in their clinical status as measured by performance status.

When this data appeared, we saw an oral agent that attacks a pathway that's pretty well understood. One of the interesting things that we've learned about this compound is not only is it really quite well tolerated, but we have been able to achieve serum testosterone levels that have now gotten into the single digits and very low. So when you traditionally use LHRH agonist therapy or bilateral orchiectomy, it's common to see patients with serum testosterone levels in the 20, 30, 40 range. Here is a compound that now we are routinely seeing serum testosterone measured in single digits.

One of the things that's actually not widely appreciated is that the assays that are used to measure serum testosterone in most of our clinical laboratories are actually much more accurate in the higher values. As you get down to the very low end, and you talk to your clinical lab people, they'll tell you that the assays aren't particularly good. So in order to measure these very low levels, new assays had to be developed because again, this was sort of territory not previously seen.

What seems to be a very well-tolerated oral agent, achieving very low levels of serum testosterone, has broad clinical activity in both patients pre- and post-chemotherapy.

Slide 22: Development of MDV3100

MDV3100 is a second generation antiandrogen. This is a small molecule that was developed by Charles Sawyers when he was at UCLA, he's now at Memorial Sloan-Kettering. So, a structurally designed second generation androgen receptor antagonist, it binds with greater affinity than with older compounds like bicalutamide. What it appears to do is it decreases the efficacy of the nuclear translocation, and that's where the action is. When the androgen receptor changes occur in the nucleus, that's when this disease becomes significantly problematic. Again, also an oral molecule. There is reasonably good evidence from animal models that this molecule, compared to older antiandrogens, demonstrates regression in patients—excuse me, in model systems in which bicalutamide-refractory disease has developed.

Slide 23: Phase I/II Study of MDV3100

So again, looking at early phase I/II studies of efficacy of this compound and again, broken down between patients who are chemotherapy-naive and in the post-chemotherapy setting—what you can see is what seems to be very interesting levels of activity as measured in terms of PSA responses, soft tissue responses, stability of bone scans and time to both PSA and radiographic progression. Again, an oral compound that seemingly has a very excellent safety profile.

Slide 24: PSA Change from Baseline

So you have two compounds that are mechanistically different, that seem to show activity both in the pre-chemotherapy and the post-chemotherapy space. Abiraterone was initially taken into a randomized trial in the post-docetaxel space. That trial rapidly accrued and has now been closed for more than a year. This drug was then taken into a pre-chemotherapy space—so again, the castrate-metastatic disease setting, mostly without symptoms. This trial has just recently stopped accrual because it accrued so rapidly. MDV3100 is in a phase III trial in the post-docetaxel setting. So we have these two compounds in late-stage clinical development, and I think many of us are clearly very optimistic that they may meet their endpoints and wind their way into clinical utility.

Slide 25: Phase III IMPACT Trial

Let's talk about the IMPACT trial—again, going back to immunomodulatory therapy, sipuleucel-T, Provenge, a therapeutic vaccine that's been around for a long time and has been tested in a couple of very small randomized trials. Some of you may remember when some of that data was taken to the FDA, and the ultimate decision by the FDA was to defer a final decision until the results of this trial, which we're about to look at, was presented.

Again, just to remind you about the design, patients who were asymptomatic or minimally symptomatic with metastatic-castrate prostate cancer—they were randomized using a 2:1 algorithm to either immediate vaccine or placebo. At the time of progression, there was the potential to cross over to a modified vaccine strategy.

Slide 26: IMPACT Overall Survival

This is a vaccine that has gone through lots of iterations and consternation, but this data was presented initially at the AUA meeting last year, which demonstrated a striking survival benefit for those patients who received sipuleucel-T. This trial was just updated at the GU meeting that I referred to in San Francisco a couple of weeks ago, and the median survival benefit has been maintained.

One of the things that many folks were interested in was when this trial was initially designed, docetaxel had not yet been approved. One of the things that clinicians are interested in is, what happened to these patients after they progressed on vaccine? What we've seen in terms of data is that the majority of patients in both the control arm as well as the experimental arm did ultimately go on to receive chemotherapy, most of them receiving docetaxel, and those arms seemed to be relatively well balanced.

This information is now at the FDA, and it is conceivable that over the next couple of months, we may hear a decision regarding an FDA approval for this vaccine. We know that it's relatively safe and easy to administer, and there is really a minimal side effect profile.

I think the one area of controversy that continues is that the mechanism of action is still a bit

unclear. This is thought to be a dendritic cell vaccine. One of the intriguing things is that in this study, there was no impact on PSA or time-to-disease progression. But yet we saw a 4-month improvement in survival.

There's a lot of issues about how we're measuring time to disease progression, recognized in prostate cancer, because it's a bone-trophic disease. It's much more difficult to look at progression-free intervals than it is in other solid tumors like lung cancer and kidney cancer, which, in most instances, those diseases provide you the ability to measure the disease objectively using CT scan imaging.

Slide 27: Docetaxel with Bevacizumab

Another trial that was completed a number of years ago was the CALGB intergroup trial, which was a randomized trial comparing patients receiving docetaxel and prednisone—standard approved therapy—versus the combination of docetaxel and bevacizumab. Prostate cancer, like a lot of epithelial cancers, has a fair amount of preclinical rationale to look at the vascular endothelial growth receptor and other mechanisms of angiogenesis. So this was a trial that was designed and conducted—now since this slide deck was actually made, we now understand, by a press release, that this study failed to meet its primary endpoint, which was overall survival. So that's what we know today. I anticipate seeing more data presented at the American Society of Clinical Oncology meetings in Chicago in June.

Slide 28: TROPIC: PHASE III Registration Study

Let me just finish off with a couple of other slides and show you what I think is some intriguing data. Again at the ASCO GU in San Francisco a couple of weeks ago, Oliver Sartor presented a randomized, phase III trial, an international clinical trial, which took patients who had metastatic-castrate progressive prostate cancer who had been treated with docetaxel-based therapy and randomly assigned to receive the second generation taxane, cabazitaxel plus prednisone, versus what many feel is a reasonable community standard of mitoxantrone and prednisone.

This therapy was moderately toxic. Again, these were patients who were heavily treated with chemotherapy, so there was a fair amount of neutropenic events. But one of the most intriguing aspects of this trial was the overall survival analysis.

Slide 29: Overall Survival with Cabazitaxel

Here you see for patients who had been previously treated with docetaxel, some of which who were to be considered refractory to docetaxel, others just previously treated with docetaxel, you see an improvement in the overall survival, saving the investigational therapy with cabazitaxel.

There are a lot of things that we don't know about this particular drug and study. Yet again, in an abstract form, we can only see so much information. I think there are many questions about whether or not cabazitaxel is a better taxane than docetaxel, whether or not retreatment with docetaxel alone would have shown us similar evidence, but those are questions that are going to need to be looked at

prospectively.

But for now, we have somewhat unexpectedly, the arrival of a new-generation taxane that seems to have very significant activity. Many of us have looked at this data and feel that perhaps that patients been less heavily treated, meaning using this compound up front, it may be that this represents a better taxane. So more to come, going forward.

Slide 30: Managing CMPC as Chronic Disease

So let me just finish off with this last slide entitled Towards the Management of Advanced Prostate Cancer as a Chronic Disease.

One of the things that is, I think, apparent to those of us who take care of this disease, is there's a very interesting disconnect. We have a disease in which the screening debate ranges, that there's lots of patients who are diagnosed early, who undergo what is hoped to be curative-intent local therapy, surgery, radiation therapy, and then there's a subset of those patients who are not cured with local therapy. As those patients go forward with PSA failure, ultimately developing clinical evidence of disease, treated with hormonal therapy and subsequent therapy, there has to be a mental shift in terms of the management. We have to move from the potential of cure with localized disease to a recognition with, at least our current therapeutic paradigm, we don't cure these patients when they develop systemic disease. But increasingly, we may be able to manage a disease that already tends to have a very long natural history with additional systemic therapy options at varying points in the disease, trying to minimize the toxicity to patients and allowing them to have optimal quality of life.

We're going to have to concentrate more heavily on understanding the biology in terms of the bone-trophic mechanism of prostate cancer and dealing with therapies that are designed to try to impact on that area.

Then we've talked about a number of very intriguing agents that are in late-stage clinical development and should some or all of these agents wind up being approved and then available to us in our armamentarium, how do we optimally integrate them into the therapeutic paradigm? How do we combine them if appropriate? How do we minimize the toxicity to the patients? Again, with the understanding that our jobs as clinicians is to optimally manage patients, but recognizing that we're not just treating a disease, we're treating a person with a disease.

It's been my pleasure this afternoon to share some thoughts about advanced prostate cancer, and that concludes my presentation at this time. Thank you.

Dr. Sherri Kramer:

Thank you, Dr. Dreicer, for that informative presentation.

Slide 31: Question-and-Answer Session

We will now begin our question-and-answer session. Dr. Dreicer, our first question is related to diagnostic testing for progressive disease. The question is, in prostate cancer patients who are treated and deemed to be disease-free, which diagnostic tests and when you do perform them when looking for disease recurrence?

Dr. Robert Dreicer:

I think that you can think about this a couple of ways. If a patient has undergone a radical prostatectomy and has an undetectable PSA post-surgery, PSA is a very good measure of the likelihood of disease recurrence. Meaning, if you have a patient who's 2 years out from a radical prostatectomy and has an undetectable PSA, there is no need to do additional diagnostic testing.

It's a little bit more complicated in the setting of patients who were treated with radiotherapy. But the reality is, it's more of an issue in those patients who actually have PSA progression. It is in that setting in which the optimal diagnostic algorithm is unclear.

I can tell you that, in my clinical practice, if I am following a patient who has a rapidly shortening PSA doubling time and I am concerned about the potential for systemic disease, I think that today the optimal test—and optimal in quotation marks—remains a bone scan and a CT scan of abdomen and pelvis. The role of MRI, SPECT, the role of PET, CT imaging remains somewhat undefined. I think we all acknowledge that these tests are of still of limited utility because of problems of sensitivity and specificity, but I think that's the best that we have currently.

Dr. Sherri Kramer:

Okay, moving on now to our next question, Dr. Dreicer. What do you think about OGX-011, the antisense drug which shows survival benefits in randomized phase II trial?

Dr. Robert Dreicer:

It's a very intriguing compound, so let me sort of just step back a bit and try to put things in perspective.

One of the things that I've learned over a long time as a clinical investigator is trying to measure my level of excitement based on clinical reality. This compound has a very strong preclinical rationale, and randomized phase II data suggest the potential for clinical activity. I remind all of us that randomized phase II trials are basically hypothesis-generating. I will just use a cautionary tale.

A number of years ago some of the audience will be familiar with a compound from Novacea, which was an interesting product based on calcium inhibition, which was taken after an enormous amount of preclinical rationale to support it, into a randomized phase II trial—a very large trial with about 250 patients. It didn't meet its primary endpoint but unexpectedly showed a survival benefit. This was, I think, very interesting to a large number of folks in the GU oncology community because it was based on large supportive preclinical data, animal model data, and then a very compelling randomized phase II.

Unfortunately, in phase III testing, the trial was stopped early, and in fact, the experimental arm was felt to be dramatically inferior to the control.

So as far as I'm concerned with regards to the antisense compound, I am very intrigued by its rationale, and I am cautiously optimistic that in phase III trials we may see benefit. But I think one has to basically do the trial, and sometimes we get answers that we don't expect.

Dr. Sherri Kramer:

Okay, very good. Our next question is an interesting one. How useful is adding antiandrogens to LHRH agonists, and should this be done prior to trying an investigational agent?

Dr. Robert Dreicer:

I think that's a very relevant clinical question. The story of what historically had been called combined androgen blockade was the question of adding an antiandrogen, usually initially to either an LHRH agonist or to patients who had undergone orchiectomy. Some of the audience may be very familiar with the era of the mid to late 90s where there were almost 20 randomized trials testing this concept.

At the end of the day, a large meta-analysis concluded that there probably was a couple of percent survival advantage to patients who were treated with combined androgen blockade as initial therapy. But the questioner asked the question about the context of using an antiandrogen in patients who have progression, presumably either biochemical progression or clinical progression, already at castrate levels of testosterone.

We certainly know that there's a small subset of patients who will manifest some level of response. There's never been a prospective test of this in a randomized trial setting. From clinical series and phase II evaluations, we had a sense that about 15% or 20% of patients may have transient responses, and the responses typically last only a few months. Therefore, while it's not unreasonable, I think that expecting big things from this particular maneuver, at least using first generation antiandrogens, is somewhat disappointing. But in the context of a patient who says "I don't want to go on a trial, I don't want chemotherapy now," is it a reasonable maneuver? I think it is. I'm hopeful that some of the data that we've sort of touched on today may obviate the use of some of these compounds and bring on more active drugs that we can use in the same setting.

Dr. Sherri Kramer:

So certainly this is an area of exciting research, as you have noted. The next question is to please further explain why you might see an overall survival benefit without a PSA response or time-to-disease progression benefit.

Dr. Robert Dreicer:

I think that there's a couple of interesting things at work here, and it's not just the sipuleucel-T data. Those of you who follow the endothelin A inhibitor status of ZD4054 would also recognize that in a randomized phase II trial, which led to a very large randomized phase III registration process, that agent also showed what appeared to be a survival benefit without impact on PSA or time to disease progression.

We have a pretty good history of a variety of compounds that may have clinical activity but seem to have a disconnect with PSA expression. Remember, PSA is a protein. We have seen instances where compounds, going back to the Suramin era, and more recently to a phase II trial done by the NCI with the compound sorafenib, where there was objective activity, meaning shrinkage of nodal disease and improvement of bone scan that was disconnected to a PSA progression. Part of the reason the FDA, I think appropriately so, has not deemed PSA response as an appropriate measure as a surrogate for response is because there's a lot of uncertainty about that sort of correlation.

The issue about PFS is interesting. I mean, as we look mechanistically at some of the compounds that we're talking about, we see survival but we don't see PFS. Recognize that that may be a limitation of our ability to measure PFS. Again, in prostate cancer, since 90% of patients with advanced disease have bone metastases, and only maybe 25% to 40% of patients will actually have nodal disease, our ability to measure change in bone with the current studies that we use—bone scan, even PET—that would look at bone reasonably well, or MRI, we don't have a good way to objectively measure progression or stability in bone. Therefore, what we look at as our inability to measure PFS may be our, in fact, our inability to see something that's actually happening.

I think it's reasonable to continue to question these issues, but at the end of the day, we've established the randomized trial with survival as an unequivocal, unambiguous endpoint. When we have compounds that demonstrate survival, I think it's now our job to go back and try to understand mechanistically why we can't recognize what we think should have been there, a PSF improvement.

Dr. Sherri Kramer:

That makes perfect sense. Our next question is, in the second-line chemotherapy setting, who do you retreat with docetaxel combination or docetaxel, and what is your most common second-line drug in clinical practice, besides clinical trial?

Dr. Robert Dreicer:

I think that's also again a very practical question. I think that there is both data from Tom Beer's work using calcitriol, the compound I spoke of earlier, that suggested drug holiday with docetaxel was certainly a rationale strategy. Any experienced clinician who manages prostate cancer has clearly seen patients who are retreated respond.

I think we can make a couple of distinctions. There are patients who are primarily docetaxel-refractory. Fortunately, we don't see many of those patients, but they do occur. So a patient who has unequivocally progressed during docetaxel—and I'm not talking about PSA progression, clinical deterioration, et cetera—we wouldn't obviously retreat that kind of patient with docetaxel. I sort of

arbitrarily utilize a 2- to 3-month timeline. A patient who has received docetaxel who's had clinical benefit and some objective evidence of response, who then 2 to 3, 4 months later begins to develop clinical deterioration, there's a subset of patients in whom docetaxel retreatment will provide probably modest, but the potential for a palliative benefit.

Clearly, patients who go much longer than 3, 4, 5 months have a very high likelihood of a docetaxel benefit from retreatment.

In the absence of a clinical trial, when I've either retreated with docetaxel and the patient has now progressed, there are obviously very limited therapeutic options. I, in the current paradigm, frequently will consider using ketoconazole in patients who've not used—who have not received it previously. There are clearly some patients who will get some modest response from mitoxantrone. I think that compound is not particularly helpful in most patients who have progressed on docetaxel. The folks at the Dana-Farber and other centers have published work about carboplatin and paclitaxel, and I think that, in selected patients, that's a reasonable palliative option. But I'm really looking forward to the ability to be able to offer better drugs in this setting, based on the data that hopefully will translate into drug approval.

Again, I understand the issue about not all patients are appropriate for clinical trials, but this is an area that sort of begs for that. If abiraterone and MDV3100 wind up being approved, it's only because clinicians were able to enroll those patients on studies—that would have led to its regulatory approval.

Dr. Sherri Kramer:

You make some very good, important points that, Dr. Dreicer. As our patients continue to live longer with this disease and then potentially develop more advanced disease, we desperately need these new treatments to add to our armamentarium.

Which brings me to the next question, which is a new treatment that you mentioned, the sipuleucel-T, and if it gets approved, when will you use it clinically?

Dr. Robert Dreicer:

This is again a very good question, and let me sort of start by reminding people that as many questioners have already asked, this is a compound that does not appear to have objective activity. What that means is, is that if you're seeing a patient and it's FDA approved, who has castrate-metastatic disease and has significant disease-related symptoms, bone pain requiring opiates, et cetera, the use of sipuleucel-T is not going to change the therapeutic paradigm. You are going to have to treat that patient with docetaxel-based therapy. The administration of that therapeutic vaccine in time is not going to change when you're going to have to utilize docetaxel. So that would suggest that patients who have asymptomatic castrate-metastatic disease, again, for the most part, the population of patients enrolled on that trial will be candidates.

I think that, in my clinical practice, if this is FDA approved, when we get to a point where we have

now ascertained that the patient in fact is metastatic and is in this sort of setting of his disease, I think it would be reasonable and rationale to discuss it with the patient. Because once you've now reviewed with the patient that it doesn't have an impact on PSA progression but the patient is asymptomatic, the ability for the patient's anxiety level to sort of continue to rise will be sort of muted. I think it's likely to be used relatively early on in that subject of asymptomatic metastatic disease.

Dr. Sherri Kramer:

Very good. Moving on to our next question. How effective is oral treatment with Casodex®, combining that with a Lupron® injection?

Dr. Robert Dreicer:

Again, if we're talking about the initial use in patients who now have metastatic disease and have not been treated with ADT before, I think that the large meta-analyses that have been done suggest that there probably is about a 5% improvement in survival, compared to the use of LHRH agonist therapy alone.

I will tell you that in my own clinical practice, I've sort of moved beyond this discussion. You know, historically there were issues of the cost of the antiandrogen. Bicalutamide is a compound that is obviously widely utilized and for a long time was a commercial. Now it's generic, and therefore the cost issues have come down somewhat.

I talk about this issue with those patients who I'm starting on combined androgen blockade or—excuse me, starting on initial ADT. If a patient is comfortable with having occasional liver function tests monitored, understands that there might be some increased cost, I think it's reasonable. But I will tell you that the majority of patients who I start on ADT probably start on monotherapy. I think it's a discussion to have with patients, but I'm not sure that, in the big scheme of things, if it's a huge issue anymore.

Dr. Sherri Kramer:

Okay, great. Now we have another question about combination therapy. Are there current trials combining radiotherapy with antiandrogens?

Dr. Robert Dreicer:

If we're talking about first-generation antiandrogens, I imagine there's probably not much going on. Recognize that the audience clearly understands that there is level one evidence that supports the role of androgen deprivation therapy and external-beam radiation therapy for intermediate, high-risk patients receiving therapy. Almost all the trials that have been conducted, the androgen deprivation therapy was in fact combined androgen blockade. In that context, if a patient is receiving radiotherapy and receiving ADT, it would be in the context of combined androgen blockage. Whether going forward there's going to be investigation of the next generation antiandrogen with

radiotherapy—while I'm unaware of any ongoing study today, it would not surprise me at all that that would be an area of investigation.

Dr. Sherri Kramer:

Okay. Very interesting. We have another question related to antiandrogens. Do you think antiandrogens still work after chemotherapy, such as docetaxel failure?

Dr. Robert Dreicer:

I think that if we looked at the first-generation data, the use of a compound such as bicalutamide after docetaxel progression, I think the likelihood that a first-generation antiandrogen would provide any meaningful clinical benefit is very, very low. It's not something I tend to do in my practice at all.

We have at least phase I and II evidence that the second-generation antiandrogen MDV3100 does appear to have activity in this exact clinical setting. It is in this exact clinical setting that the current randomized trial is being conducted. We're hopeful that this compound will demonstrate a survival benefit, and the answer going forward is going to be yes.

Dr. Sherri Kramer:

Okay, and in the 24-month post-radiation prostatectomy patient with undetectable PSA, what are the risks for taking a testosterone supplement if the disease progresses later?

Dr. Robert Dreicer:

That one—I'm not sure I got the full measure of the question, but let's just sort of talk about this: testosterone supplementation. Presumably you had a patient who had localized prostate cancer, undergoes curative-intent therapy, and for other non-prostate cancer disease–related issues, has low level testosterone. If it's in that setting, one could argue that returning that patient to normal levels of testosterone by replacement would, in a sense, be putting the patient back into the same exact setting he would be in, having not had a low serum testosterone. In that clinical setting, I think that most of us would not be uncomfortable using testosterone supplementation. I think any other settings beyond that get a little bit more problematic.

Dr. Sherri Kramer:

Okay, our next question is with regard to PSA and measuring cancer activity. If PSA is not a reliable way to measure anti-prostate cancer activity, what is the best endpoint for screening new prostate cancer drugs in phase II?

Dr. Robert Dreicer:

The questioner points out one of the major therapeutic and clinical research dilemmas that those of

us who do clinical research in this area face, in that there's no validated surrogate. I will point out that there is a potential biomarker that may wind up helping us out here, and that's circulating tumor cells. Many of the audience will know that there's at least some evidence from trials that have been published to death, that in patients receiving docetaxel-based chemotherapy, changes in circulating tumor cell numbers may be a surrogate for improvement in survival. Both the abiraterone randomized trials that I've spoken about, as well as the MVD3100 trials, actually had circulating tumor cell assessment built into these studies. Should one of those trials show survival benefit and should circulating tumor cell numbers correlate with survival, it is conceivable that that may become an important biomarker.

Unfortunately, PSA is not likely to be accepted by the FDA in this context. We're obviously very hopeful that this biomarker or perhaps others that are in development may ultimately give us an ability to get a much better handle on which drugs need to move forward into phase III development.

Dr. Sherri Kramer:

Our next question relates to antiandrogens and LHRH again. How do you time the antiandrogen with LHRH inhibition? Do you pretreat with the antiandrogen?

Dr. Robert Dreicer:

So I think that's also a very clinically practical question. In the majority of the patients that I will use a combined androgen blockade, I have no issue with starting the bicalutamide on the same day I administer LHRH agonist therapy. Remember that the testosterone flare that's induced by LHRH agonist therapy doesn't occur for 10 to 21 days. Therefore you have ample coverage with this agent by starting it the same day. I don't see any particular reason to start this therapy—it's typically inconvenient to have a patient in clinic, give them a script for bicalutamide, and have to have them come back for an injection. So I start them on the same day.

Dr. Sherri Kramer:

The next question is a question about watching and waiting. Is there a trend in treating chemical progression (ie, PSA) in the absence of documented disease on CT? Is this wise to wait until definitive disease shows up on imaging?

Dr. Robert Dreicer:

This dilemma is a very common clinical problem. It's actually a very uniquely American clinical problem because of our widespread use of PSA. This is a complicated clinical scenario, so let me try to summarize briefly my approach to this.

Androgen deprivation therapy in the non-metastatic setting is not benign. I think we are increasingly aware of ADT-related issues, such as metabolic syndrome, unequivocal increase in the risk of diabetes. We're aware of the issues about increasing osteoporosis and, in some instances,

osteoporotic-related fracture.

I think that in the absence of clear evidence that early ADT and biochemical failure changes outcome, the strategy should be expectant management. This requires this dance that we talked about earlier in trying to move a patient from a curative strategy to a chronic disease management strategy. It's much harder to have this discussion with a patient who's starting hormonal therapy. I will tell you that about 40% of my clinical practice is exactly this setting. It's a little frustrating, it's time-consuming, but again, if you think about managing disease chronically, it becomes easier to justify to the patient why early initiation of androgen deprivation therapy is not always the right thing to do.

Dr. Sherri Kramer:

Great answer. At this time we have reached our allotted time for questions and answers. If you have a question that was not answered today, please visit www.prostateeducation.com and click on Ask a Colleague. This concludes the continuing education webcast, *Castrate-Metastatic Prostate Cancer: Therapeutic Considerations for Advanced Disease.*

Slide 32: Obtaining CME Credit

END