Prostate Cancer™ UPDATE

Conversations with Urologic Oncology Investigators

Bridging the Gap between Research and Patient Care

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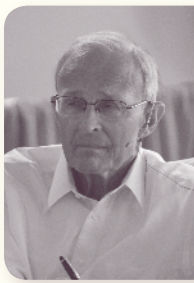
SPECIAL ISSUE

Proceedings from a Clinical Investigator Think Tank



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Prostate Cancer Update
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OVERVIEW OF ACTIVITY

An estimated 220,000 new cases of prostate cancer are diagnosed each year in the United States, and they account for approximately one third of new cancer diagnoses among men. Published results from numerous clinical trials lead to the emergence of new systemic therapies, along with changes in the indications for existing treatments. To bridge the gap between research and patient care, this program features a roundtable discussion with leading investigators to assist urologists, radiation oncologists and medical oncologists with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Communicate the benefits and risks of taxane-based chemotherapy regimens to patients with metastatic, castration-resistant prostate cancer (CRPC).
- Recognize the existing and evolving role of bone-targeted therapies, such as RANK ligand inhibitors, bisphosphonates or SERMS, for patients with prostate cancer.
- Educate patients with prostate cancer about the potential short- and long-term toxicities associated with androgen-deprivation therapy.
- Cite the mechanistic diversity of and early clinical findings with novel anti-angiogenic therapeutic approaches.
- Identify the clinical and laboratory characteristics of the neuroendocrine transformation of prostate cancer.
- Summarize emerging efficacy and safety data for endothelin A targeted, anti-angiogenic and immunotherapeutic agents under investigation for the management of CRPC.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Discuss the controversies surrounding prostate cancer screening with patients when deciding whether to obtain a PSA test.

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SELECT EXCERPTS FROM THE DISCUSSION

DR LOVE: Matt, can you discuss some of the new research relating to bone biology?

DR SMITH: One of the most exciting advances related to understanding the basic biology of the bone has been the recognition of the receptor activator of nuclear factor-kappaB (RANK) ligand as a critical mediator of osteoclast differentiation and survival.

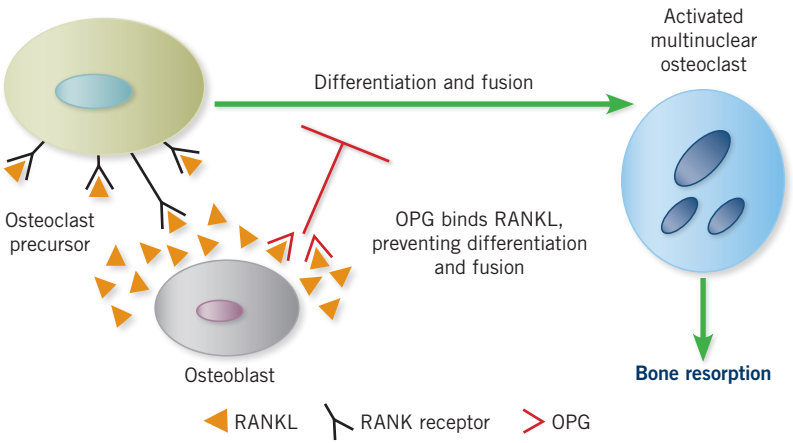
DR LOVE: Can you explain the RANK ligand pathway (1.1)?

DR SMITH: All of the signals that activate osteoclasts — the bone-resorbing cells — are mediated through the osteoblasts, which build bone. The RANK ligand pathway facilitates cross talk between osteoblasts and osteoclasts.

Many of the key signals that affect bone metabolism — parathyroid hormone, vitamin D, gonadal steroids — mediate through the osteoblast rather than the osteoclast. RANK ligand is the critical mediator of these physiologic signals that regulate bone remodeling.

These physiologic signals have their respective receptors on osteoblasts, which then turn on RANK ligand expression. The brake to this system, osteoprotegerin, feeds back and inactivates RANK ligand.

1.1 **The RANK Ligand Pathway Regulates Bone Resorption**



RANK ligand (RANKL) is required for normal osteoclast formation, function and survival. Osteoprotegerin (OPG) binds to RANKL and prevents its interaction with the RANK receptor, thereby preventing osteoclast differentiation and activity. Denosumab functions similarly to OPG, binding to RANKL and inhibiting osteoclast differentiation and survival.

DR LOVE: Where do the bisphosphonates and denosumab fit into that biology?

DR SMITH: Bisphosphonates adsorb to bone and are taken up by osteoclasts. They have different mechanisms of action according to their relative potencies. They induce osteoclast apoptosis. Hence, they inhibit osteoclast activity and kill osteoclasts.

Denosumab is a human monoclonal antibody that binds to the critical regulator, RANK ligand, and by doing so inhibits osteoclast differentiation and survival. Put simply, it's a potent osteoclast inhibitor that acts by a completely different mechanism than the bisphosphonates.

DR LOVE: Would you review the clinical trial data with denosumab?

DR SMITH: Two large, randomized, placebo-controlled trials of denosumab have been reported. The FREEDOM trial, which enrolled close to 8,000 postmenopausal women with osteoporosis, demonstrated that denosumab markedly increased bone mineral density (BMD) and dramatically reduced fractures (Cummings 2009).

The second trial, which enrolled about 1,500 men receiving androgen-deprivation therapy (ADT) for nonmetastatic prostate cancer, found that denosumab significantly increased BMD at all skeletal sites and significantly reduced the incidence of new vertebral fractures. At two years, the increase in BMD at the lumbar spine was about six or seven percent. At three years, denosumab reduced new vertebral fractures by about 62 percent (Smith 2009a; [1.2]).

A third, smaller trial evaluated denosumab in women who were receiving an adjuvant aromatase inhibitor for breast cancer. The study, designed to evaluate BMD and not large enough to evaluate fractures, demonstrated a similar benefit in BMD (Ellis 2008).

The ASCO abstract we presented evaluated the comparative results of the breast and prostate cancer studies. We saw a similar magnitude of benefit in BMD between women receiving an aromatase inhibitor for breast cancer and men receiving ADT for prostate cancer (Smith 2009b).

Head-to-head trials — one in breast cancer, one in prostate cancer and one in other common solid tumors — comparing denosumab to zoledronic acid for the prevention of skeletal-related events (SREs) are underway.

SREs, which is clinical trial jargon meant to capture the clinical complications of bone metastases, include pain that requires radiation therapy or surgery, pathologic fractures and spinal cord compressions.

The studies were designed primarily to show noninferiority with a key secondary analysis to show superiority. A recent press release reported the top-line data from the trial of approximately 2,000 patients with metastatic breast cancer. Denosumab was superior to zoledronic acid, with an 18 to 23 percent reduction in SREs (Amgen Inc 2009).

DR LOVE: What is the schedule and method of administration for denosumab?

DR SMITH: In metastatic disease, the schedule of administration is monthly,

which is the same as zoledronic acid. The route of administration is different — subcutaneous rather than intravenous.

DR LOVE: Any side effects or allergic reactions associated with denosumab?

DR SMITH: No allergic reactions. The safety data appear excellent, with no renal toxicity. In the press release, low rates of osteonecrosis of the jaw (ONJ) were reported with both zoledronic acid and denosumab (Amgen Inc 2009).

DR LOVE: What are some of the other bone-protective agents that have been evaluated in men with prostate cancer?

DR SARTOR: Another compound, toremifene — a SERM — was evaluated in a prospective, randomized fracture-prevention trial for men receiving ADT for nonmetastatic prostate cancer. That trial was also positive.

One of the potential advantages of toremifene is that it reduced hot flashes and restored some of the lipid profiles that were adversely affected by ADT (Barnette 2008; [1.3]).

DR LOVE: Matt, would you review this toremifene study conducted by your group?

DR SMITH: It had a similar design to the denosumab fracture-preven-

1.2

HALT Prostate Cancer Study: Denosumab versus Placebo for Men Receiving Androgen Deprivation Therapy

Increase in bone mineral density with denosumab compared to placebo at 24 months

Lumbar spine	6.7%*
Total hip	4.8%*
Femoral neck	3.9%*
Distal third of radius	5.5%*

* $p < 0.001$

Cumulative incidence of new vertebral fractures

	Denosumab (n = 679)	Placebo (n = 673)	*p*-value
12 months	0.3%	1.9%	0.004
24 months	1.0%	3.3%	0.004
36 months†	1.5%	3.9%	0.006

† Relative risk (95% confidence interval) = 0.38 (0.19-0.78)

"In this study of men receiving androgen-deprivation therapy for prostate cancer, a significant increase in bone mineral density was seen with denosumab at all measured skeletal sites, including the lumbar spine, hip, and radius. Denosumab was associated with significant decreases, as compared with placebo, in the cumulative incidence of new vertebral fractures at 12, 24, and 36 months."

SOURCE: Smith MR et al; Denosumab HALT Prostate Cancer Study Group. *N Engl J Med* 2009a;361(8):745-55.

tion study, with about 1,400 patients who were receiving ADT for prostate cancer. The study selected patients who were at somewhat greater risk for fracture based on older age or low baseline BMD. The participants in this two-year trial were randomly assigned to toremifene — an oral agent that is similar to tamoxifen — or placebo (Smith 2009a).

We observed that toremifene decreased new vertebral fractures by about 69 percent at two years. As Oliver commented, we also observed significant improvements in lipid profiles. In other secondary analyses, fewer hot flashes and fewer breast symptoms tended to occur in men who received toremifene (Barnette 2008; [1.3]).

DR LOVE: Laurie, what do you think about these bone-targeted therapies?

DR KLOTZ: Urologists, by and large, have been slow to embrace zoledronic acid, mainly because it was cumbersome to administer. The studies used it every three weeks, but it doesn't have to be administered that often for the prophylaxis of loss of BMD. Many are waiting with bated breath to see the denosumab data, and I believe the SERMs have a future. ■

1.3

Phase III Randomized Trial of Toremifene versus Placebo for the Prevention of Fractures and Other Adverse Effects Associated with Androgen Deprivation Therapy in Men with Prostate Cancer

"Toremifene 80 mg significantly decreased the risk of new morphometric vertebral fractures in men receiving ADT for prostate cancer. Toremifene also significantly increased BMD of the spine, total hip and femoral neck, improved lipid profiles, and decreased breast pain and frequency of hot flashes."

BMD = bone mineral density

SOURCE: Barnette G et al. *Urology* 2008;72(Suppl 5A):62-3.

SELECT PUBLICATIONS

Amgen Inc. **Denosumab demonstrates superiority over Zometa® in pivotal phase 3 head-to-head trial in breast cancer patients with bone metastases** [press release]**.** July 7, 2009.

Barnette G et al. **Multicenter phase III randomized controlled trial of toremifene to prevent fractures and other adverse effects of androgen deprivation therapy in men with prostate cancer.** *Urology* 2008;72(Suppl 5A):62-3.

Coetzee M, Kruger MC. **Osteoprotegerin-receptor activator of nuclear factor-kappaB ligand ratio: A new approach to osteoporosis treatment?** *South Med J* 2004;97(5):506-11.

Cummings SR et al; FREEDOM Trial. **Denosumab for prevention of fractures in postmenopausal women with osteoporosis.** *N Engl J Med* 2009;361(8):756-65.

Ellis GK et al. **Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer.** *J Clin Oncol* 2008;26(30):4875-82.

Smith MR et al; Denosumab HALT Prostate Cancer Study Group. **Denosumab in men receiving androgen-deprivation therapy for prostate cancer.** *N Engl J Med* 2009a;361(8):745-55.

Smith MR et al. **Effect of denosumab on bone mineral density (BMD) in women with breast cancer (BC) and men with prostate cancer (PC) undergoing hormone ablation therapy.** *Proc ASCO* 2009b;**Abstract 9520**.

DR LOVE: Mike, would you review the recent publications evaluating the duration of ADT used in combination with radiation therapy?

DR ZELEFSKY: I believe radiation oncologists, medical oncologists and urologists should be familiar with a couple of important trials evaluating the duration of ADT.

The most important trial is EORTC-22961, which randomly assigned patients with high-risk prostate cancer to six months versus three years of ADT in combination with radiation therapy. The study demonstrated that the shorter course appears to be inferior to the longer course of ADT (Bolla 2009; [2.1]).

Other studies are also suggesting that longer courses of hormonal therapy are important when radiation therapy is used for patients with high-risk disease. In RTOG-8531, patients were supposed to receive long courses of ADT with radiation therapy, but not all of them did.

In a subset analysis of patients stratified according to actual duration of hormonal therapy — one year or less versus one to five years versus more than five years — patients who received the longer courses had a survival benefit (Souhami 2009; [2.2]).

I believe the emerging notion is that for patients with high-risk disease

2.1

EORTC-22961: A Phase III Randomized Trial of Radiation Therapy with Six Months versus Three Years of Androgen Deprivation Therapy (ADT) for Locally Advanced Prostate Cancer

Five-year mortality

	Three years ADT[1] (n = 487)	Six months ADT[2] (n = 483)	Hazard ratio	*p*-value
Overall	15.2%	19.0%	1.42	0.65[3]
Prostate cancer	3.2%	4.7%	1.71	0.002
Cardiac related	3.0%	4.0%	NR	NS

[1] [LHRH agonist + flutamide/bicalutamide] x 6 months + LHRH agonist x 2.5 years;
[2] [LHRH agonist + flutamide/bicalutamide] x 6 months; [3] For noninferiority;
NR = not reported; NS = not significant

"We found that at 5 years, overall mortality was higher with short-term androgen suppression than with long-term suppression, as was prostate-cancer-specific mortality (increased by 3.8% and 1.5%, respectively).

We recommend radiotherapy plus long-term androgen suppression for men with locally advanced prostate cancer (classified as stage T2c or above, with a WHO performance status of 0 to 2) who have no contraindicating coexisting conditions."

SOURCE: Bolla M et al. *N Engl J Med* 2009;360(24):2516-27.

who are receiving radiation therapy, a long course of ADT is needed to achieve a survival benefit.

DR LOVE: What do you tell your patients about the duration of ADT?

DR KLOTZ: I tell them that if they have significant morbidity and side effects from ADT, we can discuss discontinuing the drugs earlier than three years, particularly if they have intermediate-risk disease. Otherwise, they will receive three years of therapy.

DR ZELEFSKY: I follow the patients in terms of their quality of life and how well they're tolerating the hormonal therapy. If they are miserable, I have a discussion with them and elect to terminate the hormonal therapy sooner.

These randomized trials used the relatively lower dose of radiation therapy of 70 Gray. Now in this era of dose escalation, in which we are routinely using 78 or 80 Gray for locally advanced disease, the question becomes, are these studies of duration of ADT applicable in the setting of dose escalation? We don't know the answer.

DR LOVE: Matt, would you discuss the adverse effects associated with ADT?

DR SMITH: It's clear that ADT results in increased fat mass and abdominal girth, which is what men complain about first. We have shown that ADT increases fat mass, primarily subcutaneous fat. This is not simply a cosmetic issue, and metabolic consequences occur, such as elevated triglycerides and cholesterol and decreased insulin sensitivity (Saylor 2009).

DR LOVE: Is this a classic metabolic syndrome or something different?

DR SMITH: This is a metabolic syndrome, but it's not *the* metabolic syndrome. Clear differences exist between this and the classically defined metabolic syndrome. They share insulin resistance and increased abdominal girth and triglycerides. Almost everything else is different (Smith 2008).

Metabolic syndrome increases visceral fat. ADT increases subcutaneous fat. Metabolic syndrome involves low HDL. ADT increases HDL. Additionally, other markers are different. Metabolic syndrome involves low adiponectin and high C-reactive protein levels. With ADT, adiponectin levels are high and C-reactive protein levels do not change (Smith 2008).

2.2

RTOG-8531: Effect of Duration of Androgen Deprivation Therapy in Patients with Locally Advanced Prostate Cancer Treated with Radiation Therapy

"In summary, in this hypothesis-generating exercise, our results from a secondary analysis of RTOG 85-31 protocol show that prolonged HTD [hormonal therapy duration] with LHRH agonist for more than 5 years might be associated with improved outcomes in patients with locally advanced localized prostate cancer. Together with the recent results of the EORTC 22961 randomized trial, our data suggest that decreasing the duration of hormonal administration may have a detrimental effect in these patients."

SOURCE: Souhami L et al. *J Clin Oncol* 2009;27(13):2137-43.

DR LOVE: What advice would you provide to a patient who was about to begin three years of ADT?

DR SMITH: I advise men that fractures, obesity, diabetes and possibly cardiovascular disease are real risks, but they are not inevitable consequences of treatment. Although we increase the risk of these common comorbid medical conditions, it is not inevitable that every man receiving ADT will develop them.

The risks for some of these outcomes are modest, particularly that of cardiovascular disease. Some of them are preventable, as we talked about with fractures. We need to consider the whole patient and the concept of survivorship. But I do believe we need to consider these risks, particularly as patients receive long-term therapy.

DR LOVE: I'm surprised by your comment about cardiovascular disease. Many are concerned about it and believe that it's common.

DR SMITH: In a landmark study, Nancy Keating and I reported that ADT with GnRH agonists is associated with a greater risk for a new diagnosis of diabetes and cardiovascular disease (Keating 2006).

The observation about diabetes has been confirmed in subsequent studies. The issue of cardiovascular disease is more complicated. We've seen the same results with a different database in terms of new diagnoses of cardiovascular disease. However, Dr Alibhai demonstrated an increased risk of diabetes but no increased risk for cardiovascular disease with ADT (Alibhai 2009).

It's important to note that in our analysis of the SEER-Medicare database, the relative risk was fairly modest. These are conservative estimates by the design of the trial, but we observe less than a 20 percent increase in relative risk (Keating 2006).

This observation of greater cardiovascular disease risk, in a study that included more than 70,000 patients, led to a variety of attempts to determine whether ADT is associated with greater cardiovascular mortality.

Now, let's think this through. If the risk of developing a disease increases by 20 percent, we can reasonably assume that all those events are not fatal. To evaluate mortality, you would have to design a trial that would have the power to evaluate a zero to 15 percent increase in mortality, but no such trial has been conducted.

Several analyses by a variety of groups have nearly all shown no increase in cardiovascular mortality (Efstathiou 2009; Roach 2008). A few trials have reported greater cardiovascular mortality (Tsai 2007), but in every case it was restricted to specific subsets, not to the overall patient population.

DR KLOTZ: Again, I want to reinforce Matt's comment that this is a metabolic syndrome, not *the* metabolic syndrome. It seems to me as if it's not nearly as dangerous an entity as *the* metabolic syndrome. Maybe the HDL or the lack of visceral fat is protective. The randomized trial of early versus deferred hormonal therapy by Studer demonstrated about a 10 percent improvement in other-cause mortality with early hormonal therapy (Studer 2006).

DR ZELEFSKY: Matt, do you recommend a baseline stress test before starting a patient with preexisting cardiovascular disease on a two- or three-year course of hormonal therapy?

DR SMITH: I do not. I'd advise them to see the doctor who's managing their cardiovascular disease, and I would communicate directly with that physician — either a cardiologist or an internist — about the planned treatment and the expected side effects.

The other physician will then understand why the patient's cholesterol is not as well controlled once he is receiving ADT and why the patient, whom they've been carefully advising about weight loss, is now gaining weight.

DR ZELEFSKY: If these patients have serious coronary artery disease at baseline, would your recommendation be to limit the duration of hormonal therapy?

DR SMITH: In certain cases I have done that. Although we can conclude that longer-term hormonal therapy in combination with radiation therapy improves survival (Bolla 2009; [2.1]), we can also agree that the magnitude of that benefit is relatively small and you must consider the tradeoffs.

Ultimately, we are responsible for deciding whether the patient needs treatment and the duration of treatment. I like to put the internist or cardiologist in the position of optimizing their medical management of the underlying cardiovascular disease. ■

SELECT PUBLICATIONS

Alibhai SM et al. **Impact of androgen deprivation therapy on cardiovascular disease and diabetes.** *J Clin Oncol* 2009;27(21):3452-8.

Bolla M et al. **Duration of androgen suppression in the treatment of prostate cancer.** *N Engl J Med* 2009;360(24):2516-27.

Efstathiou JA et al. **Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31.** *J Clin Oncol* 2009;27(1):92-9.

Keating NL et al. **Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer.** *J Clin Oncol* 2006;24(27):4448-56.

Roach M 3rd et al. **Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: Long-term results of RTOG 8610.** *J Clin Oncol* 2008;26(4):585-91.

Saylor PJ, Smith MR. **Metabolic complications of androgen deprivation therapy for prostate cancer.** *J Urol* 2009;181(5):1998-2006.

Smith MR et al. **Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer: Differences from the classic metabolic syndrome.** *Cancer* 2008;112(10):2188-94.

Souhami L et al. **Impact of the duration of adjuvant hormonal therapy in patients with locally advanced prostate cancer treated with radiotherapy: A secondary analysis of RTOG 85-31.** *J Clin Oncol* 2009;27(13):2137-43.

Studer UE et al. **Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) trial 30891.** *J Clin Oncol* 2006;24(12):1868-76.

Tsai HK et al. **Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality.** *J Natl Cancer Inst* 2007;99(20):1516-24.

ANTI-ANGIOGENIC AGENTS

DR LOVE: What do we know about the addition of new agents to docetaxel as first-line therapy for metastatic, castration-resistant prostate cancer?

DR SARTOR: Ever since docetaxel was approved, the hope has been that we'd be able to add something to it and obtain a better outcome. CALGB-90401 (3.1) completed accrual in December 2007 and will be reported in the near future. It is evaluating docetaxel in combination with prednisone with or without bevacizumab.

DR LOVE: What do we know about bevacizumab for prostate cancer?

DR SARTOR: In terms of clinical data, a nonrandomized Phase II trial of docetaxel with bevacizumab demonstrated reasonable prolonged progression-free survival data, but since it wasn't randomized it is hard to interpret. Then in the docetaxel-refractory setting, surprisingly a report demonstrated that patients with disease refractory to docetaxel would respond to docetaxel/bevacizumab (Di Lorenzo 2008; [3.2]).

DR LOVE: Matt, what do we know about the side effects associated with bevacizumab?

DR SMITH: We'll obviously have to await the results from CALGB-90401 to find out what they are in this patient population, but I expect they will be comparable to what has been seen in breast cancer, perhaps a little worse because our patients are older and have received other therapies.

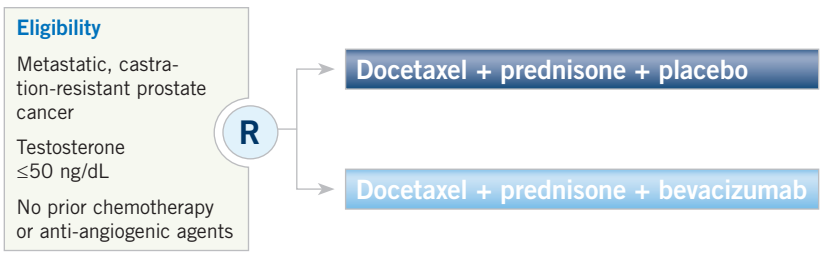
DR LOVE: Oliver, what has been observed in the other prostate cancer trials in terms of proteinuria, hypertension and nosebleeds?

DR SARTOR: My take is that they're manageable, but one issue reported

3.1

CALGB-90401: A Phase III Randomized Trial of Docetaxel/Prednisone with or without Bevacizumab

Protocol IDs: CALGB-90401, ECOG-90401, NCT00110214
Accrual: 1,020 (Closed)



SOURCE: NCI Physician Data Query, September 2009.

by the NCI could be a surprise. They evaluated the combination of docetaxel/prednisone/thalidomide/bevacizumab with zoledronic acid and reported extraordinary response rates. However, the incidence of ONJ exceeded 10 percent (Aragon-Ching 2009), which was far higher than seen before.

In an older population, it's conceivable that we could have some side effects we didn't anticipate in terms of the proteinuria and hypertension. Some deep vein thromboses and arterial thrombotic events will also occur. I believe those will be anticipated and manageable. Until we see the data, I am cautiously optimistic.

DR LOVE: Laurie, another issue with bevacizumab has been wound healing.

DR KLOTZ: This issue has arisen in kidney cancer, although it's not a big issue. Anecdotal cases, mostly of patients undergoing surgery while receiving those drugs or immediately after discontinuing them, suggest that patients do not have an excessive problem with wound healing. I haven't had that experience with a patient yet.

DR LOVE: Mike, what do we know about combining bevacizumab with radiation therapy?

DR ZELEFSKY: A lot of interest exists, and some animal studies have demonstrated radiosensitivity. At our institution, we have used bevacizumab in combination with radiation therapy for gliomas. The preliminary results appear promising for that group of patients.

3.2

Phase II Trial of Bevacizumab/Docetaxel for Docetaxel-Pretreated, Castration-Resistant Prostate Cancer

"Our results show that the combination of bevacizumab and docetaxel is active and well tolerated. Our study represents the first investigation with the bevacizumab-docetaxel combination in pretreated patients with HRPC. The most interesting finding is that seven major PSA responses were observed in previous responders to docetaxel alone, showing that bevacizumab could return activity to docetaxel."

SOURCE: Di Lorenzo G et al. *Eur Urol* 2008;54(5):1089-94.

ENDOTHELIN A RECEPTOR ANTAGONISTS

DR LOVE: What other strategies are being evaluated in combination with docetaxel as first-line therapy for metastatic, castration-resistant prostate cancer?

DR SARTOR: A number of trials are now in progress. A compound called ZD4054, which is an endothelin A receptor antagonist, had some provocative results in a randomized Phase II monotherapy trial (James 2009; [3.3]).

DR LOVE: Can you explain how ZD4054 works?

DR SARTOR: Endothelin is a compound that is present in the circulation, the prostate and other tissues. It interacts with two receptors — endothelin A and endothelin B.

DR SMITH: It's a normal regulatory protein thought to be involved in the perception of pain. It is present in the bone microenvironment, and for reasons that aren't well understood, it's synthesized in high concentrations in the prostate.

Early work by Joel Nelson and others evaluated its role in prostate cancer and found that patients with higher-grade and metastatic prostate cancer had higher serum levels of endothelin 1. At the time, Abbott Pharmaceuticals was developing an endothelin A receptor antagonist — atrasentan — for their cardiovascular program, and Joel Nelson approached the company about evaluating this agent as treatment for prostate cancer.

DR LOVE: What did we learn about atrasentan, Oliver?

DR SARTOR: As monotherapy, unfortunately, it did not have enough of an effect. The bottom line was it did not affect survival (Nelson 2008).

Atrasentan is one of the agents being evaluated in combination with docetaxel today in SWOG-S0421. Two other trials — ENTHUSE-M1C and ENTHUSE-M0 — are evaluating ZD4054 in combination with docetaxel.

DR SMITH: Atrasentan is a fairly specific endothelin A receptor inhibitor, but ZD4054 is more selective and potent at the same target.

DR LOVE: What side effects and toxicities are seen with the endothelin A receptor antagonists?

DR SARTOR: Headaches, nasal stuffiness, pedal edema and a potentially increased risk of congestive heart failure from fluid retention. But the endothelin A receptor antagonists are well tolerated overall.

3.3

Phase II Randomized Trial Comparing Two Doses of ZD4054 to Placebo for Metastatic, Castration-Resistant Prostate Cancer

"This study found no statistically significant difference between ZD4054 and placebo for the primary end point of time to progression. Nevertheless, a promising signal for prolonged overall survival compared with placebo was observed for both doses of ZD4054."

SOURCE: James ND et al. *Eur Urol* 2009;55(5):1112-23.

IMMUNOTHERAPY

DR LOVE: Paul, would you review what we know about the immunotherapeutic agent sipuleucel-T, including the recent Phase III data you just reported at the AUA meeting?

DR SCHELLHAMMER: In the Phase I and Phase II studies of sipuleucel-T, safety was confirmed and occasional PSA responses were observed (Small 2000). A small Phase III trial — D9901 — randomly assigned approximately 120 patients with asymptomatic, metastatic, castration-resistant prostate cancer in a two-to-one ratio to receive three infusions of sipuleucel-T or placebo. The primary endpoint of time to disease progression was not met, but a prespecified three-year evaluation of overall survival was highly statistically significant (Small 2006).

Our IMPACT trial was a similar protocol, with a primary endpoint of overall survival. The trial enrolled 512 patients from approximately 30 to 40 sites throughout the United States. At the time of disease progression, the patients in the control arm had the option of receiving salvage therapy with sipuleucel-T (Schellhammer 2009).

The overall survival curves showed a statistically significant benefit of 4.1 months for the patients who received sipuleucel-T. Median overall survival was 25.8 months for patients receiving sipuleucel-T and 21.7 months for those on placebo. The *p*-value was 0.032 and the hazard ratio was 0.775. It is a mature trial with a median follow-up of three years (Schellhammer 2009; [3.4]).

A number of subgroup analyses were performed, all of which favored sipuleucel-T. The one that was most critically evaluated was subsequent treatment with docetaxel, because we all know that has a survival advantage. Neither the delivery of docetaxel nor the time of its delivery altered the hazard ratio or the statistical significance (Schellhammer 2009).

The side effects associated with sipuleucel-T were mainly a mild transfusion reaction with some fever and chills that were easily controlled by acetaminophen and diphenhydramine. Only one percent of patients withdrew because of toxicity, which contrasts significantly with chemotherapy trials, in which the withdrawal rate related to side effects can be 15 percent or more (Schellhammer 2009; [3.4]).

DR LOVE: Were objective responses observed?

DR SCHELLHAMMER: Objective responses were rarely seen and PSA response was not one of the endpoints. When one studies the data from D9901 and the IMPACT trial in an integrated fashion, a significantly impressive consistency in median

3.4

IMPACT: A Phase III Randomized Trial of Sipuleucel-T versus Placebo for Metastatic, Castration-Resistant Prostate Cancer

	Sipuleucel-T (n = 341)	Placebo (n = 171)	Hazard ratio (95% CI)	*p*-value
Median overall survival	25.8 months	21.7 months	0.775 (0.614-0.979)	0.032
Median prostate cancer survival	NR	NR	0.772	0.036
Three-year survival	31.7%	23.0%	—	—
Median time to progression	NR	NR	0.951 (0.770-1.170)	0.628

CI = confidence interval; NR = not reported

"Sipuleucel-T is the first active cellular immunotherapy to demonstrate a statistically significant and clinically meaningful improvement in overall survival for cancer, and demonstrates a favorable benefit to risk profile. It has the potential to create a new paradigm for the treatment of advanced prostate cancer."

SOURCE: Schellhammer PF et al. *Proc AUA* 2009;**Late Breaking Abstract 9**.

overall survival benefit is seen. The three-year overall survival was 32 percent for sipuleucel-T and 23 percent for placebo (Schellhammer 2009).

DR LOVE: If sipuleucel-T were available, would you use it?

DR SCHELLHAMMER: If it were available, and I hope it becomes available, I would use it readily and quickly for patients who meet the criteria, namely with metastatic, castration-resistant disease.

DR LOVE: Would you use it before docetaxel?

DR SCHELLHAMMER: I would.

DR LOVE: Oliver?

DR SARTOR: I agree with Paul.

DR LOVE: Are other trials ongoing with sipuleucel-T?

DR SCHELLHAMMER: Three other trials are ongoing. One — PROTECT — was initiated several years ago for patients with rising PSA levels after radical prostatectomy and ADT. The patients were randomly assigned to either sipuleucel-T or placebo. A preliminary assessment indicated a favorable effect on PSA kinetics, but the results for the long-term endpoint of progression to metastatic disease are still not available.

A neoadjuvant trial — NeoACT — is currently enrolling 40 patients prior to radical prostatectomy. Patients receive three treatments with sipuleucel-T, and subsequent to radical prostatectomy they are randomly assigned to a single boost or no further boosting. Another trial — ProACT — is evaluating three different antigen concentrations of sipuleucel-T. The endpoints include CD54 upregulation — a test for efficacy, circulating tumor cells and other immunologic profiles.

HORMONAL THERAPY

DR LOVE: Can you discuss the available clinical data with abiraterone?

DR SCHELLHAMMER: Two published reports with abiraterone, an inhibitor of cytochrome P 17 (CYP17), each with approximately 50 patients, were reported from the Royal Marsden Hospital. One trial included patients who had received chemotherapy (Reid 2009) and the other enrolled those who had chemotherapy-naïve disease (Attard 2009).

Remarkable PSA responses were noted, with 15 to 20 percent of patients obtaining a greater than 90 percent decrease in PSA and 50 to 70 percent of patients having a greater than 50 percent decrease in PSA. Most impressive were the objective response rates, which were between 15 and 30 percent.

These results led to the two large ongoing trials. The first one, with abiraterone combined with prednisone versus prednisone alone for more than 1,000 patients with chemotherapy-treated disease, has completed accrual.

The other, for patients with chemotherapy-naïve, castration-resistant metastatic disease, is currently ongoing. The major side effects associated with abiraterone include fluid retention, mild hypertension and hypokalemia. ■

SELECT PUBLICATIONS

Aragon-Ching JB et al. **Higher incidence of osteonecrosis of the jaw (ONJ) in patients with metastatic castration resistant prostate cancer treated with anti-angiogenic agents.** *Cancer Invest* 2009;27(2):221-6.

Attard G et al. **Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer.** *J Clin Oncol* 2009;27(23):3742-8.

Di Lorenzo G et al. **Combination of bevacizumab and docetaxel in docetaxel-pretreated hormone-refractory prostate cancer: A phase 2 study.** *Eur Urol* 2008;54(5):1089-94.

James ND et al. **Safety and efficacy of the specific endothelin-A receptor antagonist ZD4054 in patients with hormone-resistant prostate cancer and bone metastases who were pain free or mildly symptomatic: A double-blind, placebo-controlled, randomised, phase 2 trial.** *Eur Urol* 2009;55(5):1112-23.

Nelson JB et al. **Phase 3, randomized, controlled trial of atrasentan in patients with nonmetastatic, hormone-refractory prostate cancer.** *Cancer* 2008;113(9):2478-87.

Reid AH et al. **A multicenter phase II study of abiraterone acetate (AA) in docetaxel pretreated castration-resistant prostate cancer (CRPC) patients (pts).** *Proc ASCO* 2009;**Abstract 5047**.

Schellhammer PF et al. **A randomized, double-blind, placebo-controlled, multi-center, phase III trial of sipuleucel-T in men with metastatic, androgen independent prostatic adenocarcinoma (AIPC).** *Proc AUA* 2009;**Late Breaking Abstract 9**.

Small EJ et al. **Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer.** *J Clin Oncol* 2006;24(19):3089-94.

Small EJ et al. **Immunotherapy of hormone-refractory prostate cancer with antigen-loaded dendritic cells.** *J Clin Oncol* 2000;18(23):3894-903.

PSA SCREENING

DR LOVE: Laurie, can you discuss the recently published trials evaluating PSA screening?

DR KLOTZ: Two landmark articles were published in *The New England Journal of Medicine* this year, and the trials had opposite results. In the United States, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial enrolled approximately 78,000 men and was negative with no difference in prostate cancer mortality associated with annual screening. The proportion of patients on the control arm who eventually had a PSA test, however, was more than half. The second key problem with the study was that the event rate was extremely low (Andriole 2009; [4.1]).

It's worth emphasizing that both of these studies were reported at an interim evaluation, and neither of them have been formally completed. Authors of both studies have been criticized for reporting the studies prematurely. I believe you can argue that although we have the results from these relatively mature trials, both quite large, we still don't have a definitive answer.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) enrolled around 180,000 men. It was a conglomeration from several countries with some differences in the frequency of screening

and patient eligibility. The bottom line was that PSA screening led to a 20 percent reduction in prostate cancer mortality. It was unequivocally a positive trial.

The other side of the coin was that about 1,400 men would need to be screened and 48 cases of prostate cancer would need to be treated to avoid each death from prostate cancer. The reduction in mortality was seven per 10,000 men, which is relatively modest (Schröder 2009; [4.2]).

This is one of those situations in which the glass is half empty or the glass is half full. To me, the European trial was the better trial. It didn't have the problem of contamination, and it was 2.5 times as large. It's the long-awaited, randomized trial of PSA screening showing a mortality reduction. The glass is half empty in that the number needed to screen and the number needed to treat for each death avoided were high. It has engendered a fairly intense debate concerning the issue of PSA screening.

I am on the proscreening side, but this shows us clearly that we have to be more selective about offering treatment. If the concept of selective therapy is embodied in PSA screening, it starts to become much more appealing. ■

4.1

PLCO Trial: Effect of Prostate Cancer Screening on Mortality

"We are reporting here for the first time on the PLCO trial with respect to prostate-cancer mortality. At 7 years, screening was associated with a relative increase of 22% in the rate of prostate cancer diagnosis, as compared with the control group... Screening was associated with no reduction in prostate-cancer mortality during the first 7 years of the trial (rate ratio, 1.13), with similar results through 10 years, at which time 67% of the data were complete."

SOURCE: Andriole GL et al; PLCO Project Team. *N Engl J Med* 2009;360(13):1310-9.

4.2

ERSPC: Effect of Prostate Cancer Screening on Mortality

"In an intention-to-screen analysis of data from seven European centers, PSA screening was associated with a significant absolute reduction of 0.71 prostate-cancer death per 1000 men after an average follow-up of 8.8 years (median, 9.0). This finding corresponds to a relative reduction of 20% in the rate of death from prostate cancer.... To prevent one prostate-cancer death, 1,410 men (or 1,068 men who actually underwent screening) would have to be screened, and an additional 48 men would have to be treated."

SOURCE: Schröder FH et al; ERSPC Investigators. *N Engl J Med* 2009;360(13):1320-8.

SELECT PUBLICATIONS

Andriole GL et al; PLCO Project Team. **Mortality results from a randomized prostate-cancer screening trial.** *N Engl J Med* 2009;360(13):1310-9.

Schröder FH et al; ERSPC Investigators. **Screening and prostate-cancer mortality in a randomized European study.** *N Engl J Med* 2009;360(13):1320-8.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The RANK ligand pathway is responsible for the cross talk between osteoblasts and osteoclasts.**
   a. True
   b. False

2. **Denosumab, a human monoclonal antibody that inhibits RANK ligand, has which of the following effects in men receiving androgen-deprivation therapy for nonmetastatic prostate cancer?**
   a. Increases bone mineral density at multiple skeletal sites
   b. Reduces the incidence of new vertebral fractures
   c. Both a and b
   d. None of the above

3. **Toremifene, a SERM, reduces the incidence of new vertebral fractures in men receiving androgen-deprivation therapy for prostate cancer and also _____.**
   a. Improves lipid profiles
   b. Reduces hot flashes
   c. Reduces breast pain
   d. All of the above

4. **EORTC-22961 demonstrated that _____ was better than six months of androgen-deprivation therapy for men with locally advanced prostate cancer that was treated with radiation therapy.**
   a. Two years
   b. Three years
   c. Five years
   d. None of the above

5. **Androgen-deprivation therapy may increase _____.**
   a. Subcutaneous fat
   b. Triglycerides
   c. HDL
   d. Both a and b
   e. All of the above

6. **CALGB-90401 is evaluating docetaxel/prednisone in combination with _____ for metastatic, castration-resistant prostate cancer.**
   a. ZD4054
   b. Abiraterone
   c. Bevacizumab
   d. Sipuleucel-T

7. **In a Phase II trial, some patients with docetaxel-refractory disease were found to respond to bevacizumab/docetaxel.**
   a. True
   b. False

8. **Which of the following is considered an endothelin A receptor antagonist?**
   a. ZD4054
   b. Atrasentan
   c. Abiraterone
   d. Both a and b
   e. All of the above

9. **Which of the following side effects is associated with the endothelin A receptor antagonists?**
   a. Nasal stuffiness
   b. Headaches
   c. Edema
   d. All of the above

10. **In the IMPACT trial, sipuleucel-T was found to improve _____ in men with metastatic, castration-resistant prostate cancer.**
    a. Overall survival
    b. Disease-free survival
    c. Both a and b
    d. None of the above

Post-test answer key: 1a, 2c, 3d, 4b, 5e, 6c, 7a, 8d, 9d, 10a

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Prostate Cancer Update — Think Tank Issue 1, 2009

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Effect of denosumab on bone mineral density and fracture rate among patients receiving androgen-deprivation therapy (ADT) for prostate cancer	4 3 2 1	4 3 2 1
Nonskeletal effects of toremifene in patients receiving ADT for prostate cancer	4 3 2 1	4 3 2 1
Metabolic complications associated with ADT	4 3 2 1	4 3 2 1
Activity of bevacizumab/docetaxel in patients with docetaxel-pretreated, castration-resistant prostate cancer (CRPC)	4 3 2 1	4 3 2 1
Mechanisms of action of atrasentan and ZD4054	4 3 2 1	4 3 2 1
IMPACT: A Phase III randomized study of sipuleucel-T for metastatic CRPC	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain:.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Communicate the benefits and risks of taxane-based chemotherapy regimens to patients with metastatic, castration-resistant prostate cancer (CRPC)..... 4 3 2 1 N/M N/A
- Recognize the existing and evolving role of bone-targeted therapies, such as RANK ligand inhibitors, bisphosphonates or SERMS, for patients with prostate cancer..... 4 3 2 1 N/M N/A
- Educate patients with prostate cancer about the potential short- and long-term toxicities associated with androgen-deprivation therapy..... 4 3 2 1 N/M N/A
- Cite the mechanistic diversity of and early clinical findings with novel anti-angiogenic therapeutic approaches..... 4 3 2 1 N/M N/A
- Identify the clinical and laboratory characteristics of the neuroendocrine transformation of prostate cancer..... 4 3 2 1 N/M N/A
- Summarize emerging efficacy and safety data for endothelin A targeted, anti-angiogenic and immunotherapeutic agents under investigation for the management of CRPC..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials..... 4 3 2 1 N/M N/A
- Discuss the controversies surrounding prostate cancer screening with patients when deciding whether to obtain a PSA test..... 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

- ☐ Yes, I am willing to participate in a follow-up survey.
- ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty and moderator for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Laurence Klotz, MD	4 3 2 1	4 3 2 1
A Oliver Sartor, MD	4 3 2 1	4 3 2 1
Paul F Schellhammer, MD	4 3 2 1	4 3 2 1
Matthew R Smith, MD, PhD	4 3 2 1	4 3 2 1
Michael J Zelefsky, MD	4 3 2 1	4 3 2 1
Moderator	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and moderator for this activity:

.....

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PCUTT109

Prostate Cancer™ UPDATE

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Prostate Cancer™
U P D A T E

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