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Prostate Cancer™ UPDATE

Conversations with Urologic Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

A Oliver Sartor, MD
Nancy A Dawson, MD
Anthony Zietman, MD
E David Crawford, MD

EDITOR

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CME Certified

Prostate Cancer Update
A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

An estimated 220,000 new cases of prostate cancer are diagnosed yearly in the United States and account for approximately one third of new cancer cases among men. Published results from clinical trials lead to the emergence of new local and systemic therapeutic approaches, along with changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing urologist, radiation oncologist and medical oncologist must be well informed of these advances. By providing information on the latest research developments and expert perspectives, this CME activity assists clinicians with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Appraise the clinical benefits of adjuvant radiation therapy for patients with locally advanced or high-risk prostate cancer.
- Apply the results of existing and emerging research on the choice and timing of endocrine therapy alone or with radiation therapy to the care of patients with localized, biochemically recurrent or metastatic prostate cancer.
- Communicate the benefits and risks of taxane-based chemotherapy regimens to patients with recurrent prostate cancer.
- Summarize emerging efficacy and safety data with targeted agents in castration-resistant prostate cancer, including anti-angiogenic therapy, microtubule stabilizers, specific endothelin A receptor antagonists, immunomodulatory agents and novel inhibitors of testosterone synthesis or activity.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.

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INTERVIEW

A Oliver Sartor, MD

Dr Sartor is Piltz Endowed Professor of Cancer Research and Professor of Medicine and Urology at Tulane Medical School in New Orleans, Louisiana.

Tracks 1-16

Select Excerpts from the Interview

Track 3

DR LOVE: Would you describe the mechanism of action and the efficacy and tolerability of sipuleucel-T in prostate cancer?

DR SARTOR: The mechanism of sipuleucel-T is unlike that of any other vaccine. It is tailor-made for the specific patient. Immune cells are collected from the patient and exposed to a fusion protein composed of prostatic acid phosphatase and GM-CSF. This process "teaches" the patient's immune cells to target prostatic acid phosphatase, which is specific to prostate cells. The tailor-made cellular vaccine is then administered to the patient through infusion every two weeks for three treatments.

IMPACT, a randomized, placebo-controlled study, demonstrated a survival advantage with this agent, although no effect on disease progression or response rate was observed (Kantoff 2010; [1.1]). The main potential side effects are acute-phase reactions such as fever, chills, rigors and flu-like symptoms.

DR LOVE: How do you envision the integration of sipuleucel-T with chemotherapy into the treatment of CRPC?

DR SARTOR: Chemotherapy such as docetaxel and immunotherapy such as sipuleucel-T are highly distinct treatment approaches, and I regard them as complementary therapies rather than mutually exclusive.

With respect to adverse events, chemotherapies such as docetaxel typically cause neutropenia, diarrhea and fatigue. However, with sipuleucel-T patients develop rigors and chills that might be associated with the infusion but do not experience too many side effects thereafter.

No data suggest that chemotherapy is less effective after a vaccine. Until we have more data, it is also hard to say whether chemotherapy is more effective after a vaccine. Nevertheless, I believe we should continue with our usual therapies, such as docetaxel, after disease progression on the vaccine.

Track 4

DR LOVE: Can you review what we know about another new agent, cabazitaxel, which was recently approved by the FDA for second-line treatment of castration-resistant prostate cancer (CRPC) in patients who have previously received docetaxel?

DR SARTOR: Cabazitaxel is a novel taxane that has been studied in a large Phase III trial for patients with CRPC who have experienced disease progression after docetaxel. Patients were randomly assigned to cabazitaxel/prednisone or mitoxantrone/prednisone, and the group that received cabazitaxel showed a significant improvement in survival (Sartor 2010; [1.2]).

I believe cabazitaxel will have an opportunity to move up and be compared to first-line agents such as docetaxel, particularly because it has demonstrated activity when conventional agents have failed.

DR LOVE: What about the side effects with this agent compared to other taxanes?

1.1

IMPACT: Results of Sipuleucel-T versus Placebo for Patients with Asymptomatic or Minimally Symptomatic Metastatic Castration-Resistant Prostate Cancer

	Overall survival	Three-year survival	Time to disease progression
Sipuleucel-T (n = 341)	25.8 mo	32.1%	14.6 wk
Placebo (n = 171)	21.7 mo	23.0%	14.4 wk
Hazard ratio	0.759	—	0.951
p-value	0.017	—	0.628

Kantoff P et al. Genitourinary Cancers Symposium 2010;**Abstract 8**.

1.2

TROPIC: Efficacy and Safety of Cabazitaxel/Prednisone (CBZP) versus Mitoxantrone/Prednisone (MP) for Patients with Castration-Resistant Metastatic Prostate Cancer Previously Treated with Docetaxel

Efficacy endpoints	CBZP (n = 378)	MP (n = 377)	Hazard ratio	*p*-value
Overall survival (intent-to-treat population)	15.1 mo	12.7 mo	0.70	<0.0001
Progression-free survival	2.8 mo	1.4 mo	0.74	<0.0001
Median time to progression	8.8 mo	5.4 mo	0.61	<0.0001
Response rate	14.4%	4.4%	—	0.0005
	CBZP (n = 371)		MP (n = 371)	
Select adverse events	All grades	Grade ≥III	All grades	Grade ≥III
Febrile neutropenia	7.5%	7.5%	1.3%	1.3%
Diarrhea	46.6%	6.2%	10.5%	0.3%
Fatigue	36.7%	4.9%	27.5%	3.0%
Asthenia	20.5%	4.6%	12.4%	2.4%

Sartor AO et al. Genitourinary Cancers Symposium 2010;**Abstract 9**.

DR SARTOR: Cabazitaxel is associated with Grade III and IV neutropenia, febrile neutropenia, fatigue, asthenia and diarrhea. It does not appear to be associated with neuropathy.

White blood cell growth factors were allowed in the trial, but they were not encouraged because this did not meet the ASCO guidelines for primary prophylaxis.

I believe growth factors will and should be used with this agent. No head-to-head comparison has yet been made with other taxanes, but my sense is that a little more neutropenia occurs with this agent. However, the current safety data are from the second line, and the safety profile may look a lot better in the front line because the patients are in better health.

Tracks 6, 9

DR LOVE: Anything new in the use of docetaxel for patients with metastatic CRPC?

DR SARTOR: We have learned how to better use docetaxel over time. First, one should not be quick to stop docetaxel during the initial cycles. Approximately 20 to 25 percent of patients may experience a PSA flare on treatment initiation with docetaxel, and this may not indicate disease progression.

I am committed to administering at least three cycles before making any decisions about progression and treatment failure. Another point is to use docetaxel earlier in treatment rather than after multiple secondary hormonal manipulations have failed and the patient's performance status has declined.

Additionally, although we have no trial results of docetaxel for biochemical PSA-only failures, it will probably be active in those cases. Frequently a gap occurs between the point of exhausting hormonal options and evidence of metastatic disease, and I have used docetaxel at times in this setting. If a drug is active later, it is probably active earlier too.

DR LOVE: What are your thoughts about bringing chemotherapy into the treatment algorithm in earlier stages of prostate cancer?

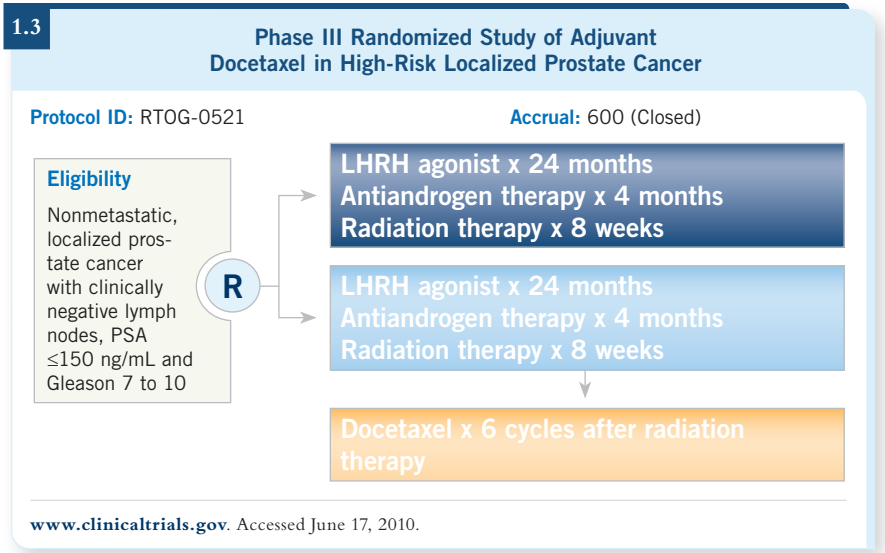
DR SARTOR: Use of chemotherapy in earlier stages of prostate cancer is investigational, and I am a co-principal investigator of RTOG-0521 (1.3), which is evaluating adjuvant docetaxel in high-risk localized prostate cancer. Patients at high risk include those with Gleason scores of seven to 10, those with high PSA levels and those with T3 or T4 disease. The current standard approach for such patients is radiation therapy and two to three years of hormonal therapy. Patients on the RTOG-0521 trial receive this standard treatment and are also randomly assigned at enrollment to no docetaxel or docetaxel for six cycles after completion of radiation therapy.

The trial has completed enrollment and is in the assessment phase. The primary endpoint is survival at four years, so it will be an additional three and a half years until we see initial results.

Track 12

DR LOVE: Is there a connection between the rate of PSA decline with hormonal therapy and prognosis?

DR SARTOR: This is an interesting topic. It is well known that a rapid rise in PSA level at diagnosis is not good. It has also been published that a rapid fall in PSA level with radiation therapy is good. So we studied the kinetics of PSA decline after hormonal therapy to determine whether a rapid decline is good or bad. For patients with low-range PSA levels, one cannot analyze this well because it is difficult to get a good handle on PSA kinetics, so this could



be done only for patients with relatively high PSA levels. We found that a rapid PSA decline after hormonal therapy imparts a poorer prognosis (Choueiri 2009).

I believe PSA kinetics and their relationship to tumor cell proliferation are key factors. If PSA increases rapidly or decreases rapidly, that suggests a rapid turnover of the tumor cells. Whether the treatment is radiation therapy or hormonal therapy, rapid tumor proliferation is not a good sign and puts the patient in a poor prognostic group. ■

SELECT PUBLICATIONS

Choueiri TK et al. **Time to prostate-specific antigen nadir independently predicts overall survival in patients who have metastatic hormone-sensitive prostate cancer treated with androgen-deprivation therapy.** *Cancer* 2009;115(5):981-7.

Kantoff P et al. **Updated survival results of the IMPACT trial of sipuleucel-T for metastatic castration-resistant prostate cancer (CRPC).** Genitourinary Cancers Symposium 2010;**Abstract 8**.

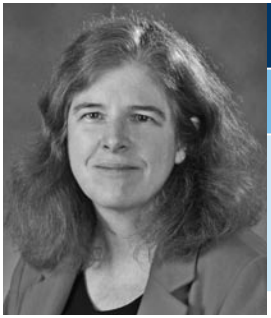
Nakabayashi M et al. **Response to docetaxel/carboplatin-based chemotherapy as first- and second-line therapy for patients with metastatic hormone-refractory prostate cancer.** *BJU International* 2008;101(3):308-12.

Petrylak DP et al. **Persistence of immunotherapy survival effects of sipuleucel-T and relationship to postrandomization docetaxel use in phase III studies.** *Proc ASCO* 2010;**Abstract 4551**.

Reuter CW et al. **Carboplatin plus weekly docetaxel as salvage chemotherapy in docetaxel-resistant and castration-resistant prostate cancer.** *World J Urol* 2010;28(3):391-8.

Sartor AO et al. **Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: Final results of a multinational phase III trial (TROPIC).** Genitourinary Cancers Symposium 2010;**Abstract 9**.

Stewart FP et al. **Correlation between product parameters and overall survival in three trials of sipuleucel-T, an autologous active cellular immunotherapy for the treatment of prostate cancer.** *Proc ASCO* 2010;**Abstract 4552**.



INTERVIEW

Nancy A Dawson, MD

Dr Dawson is William M Scholl Professor of Medicine and Oncology and Director of the Genitourinary Oncology Program at the Lombardi Comprehensive Cancer Center at Georgetown University in Washington, DC.

Tracks 1-16

Track 1 Spectrum of clinical phenotypes in castration-resistant PCa and selection of treatment

Track 2 Abiraterone acetate, a potent, oral antiandrogen that suppresses testosterone production

Track 3 Antitumor activity of the selective endothelin receptor A antagonist ZD4054 in PCa

Track 4 Tolerability of ZD4054

Track 5 Phase II randomized, placebo-controlled trial of ZD4054 for castration-resistant PCa and bone metastases

Track 6 Role of cabazitaxel after progression on docetaxel for patients with castration-resistant metastatic PCa

Track 7 Perspective on the results of CALGB-90401 combining bevacizumab with chemotherapy for metastatic castration-resistant PCa

Track 8 **Case discussion:** A 70-year-old man presents with omental metastases eight years after radiation therapy and androgen deprivation therapy (ADT) for Gleason 8 PCa

Track 9 Reintroduction of docetaxel for recurrent intra-abdominal metastases after a "treatment holiday"

Track 10 Predictors of response to docetaxel in patients with metastatic PCa

Track 11 C**ase discussion:** A 66-year-old man initially diagnosed in 1998 with locally advanced PCa develops bone metastases and responds to late-line treatment with docetaxel/bevacizumab, lenalidomide and prednisone (ART-P) on a clinical trial

Track 12 Management of bisphosphonate-associated osteonecrosis of the jaw

Track 13 Phase II trial of ART-P for the treatment of metastatic castration-resistant PCa

Track 14 Therapeutic options after progression on docetaxel for metastatic castration-resistant PCa

Track 15 Use of docetaxel for the treatment of metastatic castration-resistant PCa

Track 16 Effectiveness of ketoconazole in reversing disseminated intravascular coagulation in patients with PCa

Select Excerpts from the Interview

Track 2

DR LOVE: Would you discuss the new targeted endocrine agent abiraterone acetate?

DR DAWSON: Abiraterone is an oral drug, and it suppresses all forms of androgen. It suppresses not only testosterone and dihydrotestosterone but also the adrenal androgens. It's considered to be 10 times more potent than ketoconazole. Abiraterone can lower testosterone levels to less than one ng/mL. The other quality it possesses that no other available drug does is that it lowers the androgen levels in tissue.

In an interesting correlative science study at The University of Texas MD Anderson Cancer Center, the investigators performed bone marrow biopsies on patients who were receiving abiraterone. They were able to show that androgen levels in the bone marrow tissue declined, and the decline correlated with the patients whose disease responded to abiraterone (Efstathiou 2009).

One hypothesis with regard to castration-resistant prostate cancer (CRPC) is that patients become hypersensitive to low androgen levels and that's why their disease is breaking through. So if you can better suppress androgens and do so across the board, you'll obtain a better response, or you'll obtain a second response even though the patient is already receiving an LHRH analog.

Tracks 3-5

DR LOVE: Can you summarize what is known about the novel agent ZD4054 currently under evaluation for patients with CRPC?

DR DAWSON: ZD4054 is a specific endothelin A receptor antagonist, which is important because endothelin receptors A and B perform slightly different functions. These receptors are involved with cancer progression and are specifically important in bone. Endothelin B receptor antagonists can sometimes be detrimental. This differentiates ZD4054 from atrasentan, which is predominantly an antagonist against endothelin A receptor but is not specific for the receptor as is ZD4054. Drugs such as ZD4054 have been combined with agents such as zoledronic acid. Together they can provide more efficacy than either agent alone in decreasing the progression of bone metastases in tumor models.

DR LOVE: What is known about the efficacy of ZD4054?

DR DAWSON: Data were recently published from a randomized Phase II trial evaluating two different doses of ZD4054 versus placebo for patients with CRPC and bone metastases that were painless or mildly symptomatic.

At final analysis, an unexpected improvement in overall survival of approximately seven months was reported for patients who received ZD4054. This being a Phase II trial, overall survival was not the primary endpoint. No

improvement was observed in the primary endpoint of progression-free survival (James 2009; [2.1]). Follow-up in this trial was extended to verify this effect on overall survival, and these results inspired a randomized Phase III trial of the 10-mg dose of ZD4054 versus placebo that is now under way (NCT00626548). A Phase III trial of docetaxel with or without ZD4054 is also under way (NCT00617669).

DR LOVE: Would you discuss the results your group published on quality of life and symptoms in patients with metastatic hormone-resistant prostate cancer after treatment with ZD4054?

DR DAWSON: Most patients continued to enjoy a reasonably good quality of life throughout the course of the study. Minimal change occurred in quality of life, and no difference in quality of life was evident between patients who received ZD4054 and those who received placebo. These patients were not suffering from any significant toxicities associated with the drug (Dawson 2010). ZD4054 can cause symptoms similar to those of a mild case of the flu — patients develop a runny nose, a little edema and a little fatigue.

2.1

Efficacy of the Specific Endothelin A Receptor Antagonist ZD4054 for Patients with Hormone-Resistant Prostate Cancer (HRPC) and Minimally Symptomatic Bone Metastases

	Placebo (n = 107)	ZD4054 10 mg (n = 107)	ZD4054 15 mg (n = 98)
Median time to disease progression	3.7 months	4.6 months	3.8 months
	Reference	HR 1.09; $p = 0.553$	HR 0.94; $p = 0.702$
Median overall survival	17.3 months	24.5 months	23.5 months
	Reference	HR 0.55; $p = 0.008$	HR 0.65; $p = 0.052$

HR = hazard ratio

"Although the primary end point of time to progression was not achieved in this study, ZD4054 was associated with a promising improvement in overall survival in patients with asymptomatic or mildly symptomatic metastatic HRPC."

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

Track 7

DR LOVE: At the recent ASCO 2010 meeting, results were presented from the Phase III CALGB-90401 trial, evaluating docetaxel/prednisone with or without bevacizumab in men with metastatic CRPC, and the authors reported that despite improvements in progression-free survival, measurable disease response and post-therapy PSA decline, the addition of bevacizumab to docetaxel/prednisone did not improve overall survival (Kelly 2010; [2.2]). What are your thoughts on targeting the tumor vasculature in prostate cancer?

DR DAWSON: The Phase III trial was based on a Phase II trial also conducted by the CALGB, in which docetaxel/estramustine/bevacizumab appeared promising (Picus 2003). Unfortunately, in the Phase III setting no improvement in overall survival was evident with the addition of bevacizumab to docetaxel (Kelly 2010; [2.2]). ■

2.2

CALGB-90401: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial Evaluating Docetaxel and Prednisone with or without Bevacizumab for Men with Metastatic Castration-Resistant Prostate Cancer

Endpoint	Docetaxel/ prednisone + bevacizumab (N = 524)	Docetaxel/ prednisone (N = 526)	Hazard ratio	*p*-value
Median overall survival	22.6 months	21.5 months	0.91	0.181*
Median progression-free survival	9.9 months	7.5 months	0.77	<0.0001*
≥50% decline in PSA	69.5%	57.9%	—	0.0002
Objective response	53.2%	42.1%	—	0.0113
Grade III or higher treatment-related adverse events	74.8%	55.3%	—	<0.001
Treatment-related deaths	4.4%	1.1%	—	0.0014

* Stratified log-rank *p*-value

Kelly WM et al. *Proc ASCO* 2010;**Abstract LBA4511**.

SELECT PUBLICATIONS

Dawson N et al. **Health-related quality of life in pain-free or mildly symptomatic patients with metastatic hormone-resistant prostate cancer following treatment with the specific endothelin A receptor antagonist zibotentan (ZD4054).** *J Cancer Res Clin Oncol* 2010;[Epub ahead of print].

Efstathiou E et al. **Candidate predictors of response to abiraterone acetate (AA) in castrate-resistant prostate cancer (CRPC).** Genitourinary Cancers Symposium 2009;**Abstract 187**.

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.

Kelly WM et al. **A randomized, double-blind, placebo-controlled phase III trial comparing docetaxel, prednisone, and placebo with docetaxel, prednisone, and bevacizumab in men with metastatic castration-resistant prostate cancer (mCRPC): Survival results of CALGB 90401.** *Proc ASCO* 2010;**Abstract LBA4511**.

Lassi K, Dawson NA. **Update on castrate-resistant prostate cancer: 2010.** *Curr Opin Oncol* 2010;22(3):263-7.

Picus J et al. **The use of bevacizumab (B) with docetaxel (D) and estramustine (E) in hormone refractory prostate cancer (HRPC): Initial results of CALGB 90006.** *Proc ASCO* 2003;**Abstract 1578**.

INTERVIEW

Anthony Zietman, MD

Dr Zietman is Jenot and William Shipley Professor of Radiation Oncology at Harvard Medical School in Boston, Massachusetts.

Tracks 1-9

Track 1 Benefit of combining radiation therapy with ADT for patients with locally advanced or high-risk PCa

Track 2 Proton-beam radiation therapy for the treatment of PCa

Track 3 Emerging data on abbreviated radiation therapy dosing schedules and stereotactic radiation therapy

Track 4 **Case discussion:** A 62-year-old man with a small Gleason 6 PCa in one biopsy specimen seeks a second opinion regarding local therapy options

Track 5 Watchful waiting as a treatment option for a patient with a small, low-risk PCa

Track 6 **Case discussion:** A 72-year-old man with slowly increasing PSA levels 10 years after radiation therapy for a high-grade PCa

Track 7 Local treatment options for a slowly rising PSA after radiation therapy

Track 8 Tolerability of bicalutamide compared to LHRH agonists

Track 9 Systemic therapy options for elderly patients with PCa and a rising PSA

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: What is the current status of combined hormonal and radiation therapy for locally advanced prostate cancer?

DR ZIETMAN: In a randomized Phase III trial (Widmark 2009; [3.1]), 875 men with locally advanced prostate cancer received androgen deprivation therapy, and half of those men also received radiation therapy. With a median follow-up of approximately eight years, a clear survival advantage is evident for those who received radiation therapy in addition to the hormonal therapy.

That study has been criticized because the hormonal therapy consisted of combined blockade with an LHRH agonist for three months followed by maintenance flutamide alone — without an LHRH agonist in the maintenance setting. However, another trial (Warde 2010; [3.2]) used a lifelong LHRH agonist or bilateral orchiectomy as androgen deprivation therapy and randomly assigned patients to receive radiation therapy or not, and the

results were identical to those of the first study, showing a substantial survival improvement with the combined therapy. Combining hormonal and radiation therapy is a standard approach in locally advanced prostate cancer. However, considerable variation exists regarding the incorporation of radiation therapy, and frequently radiation therapy is not provided in clinical practice. These data remind us that the combined approach confers a survival advantage that emerges as early as five years after treatment initiation.

3.1

Efficacy of Endocrine Treatment with or without Radiation Therapy in Locally Advanced Prostate Cancer

	10-year prostate cancer-specific mortality	10-year mortality	10-year PSA recurrence
Hormonal treatment (n = 439)	23.9%	39.4%	74.7%
Hormonal treatment with radiation therapy (n = 436)	11.9%	29.6%	25.9%
Relative risk	0.44	0.68	0.16

Widmark A et al. *Lancet* 2009;373(9660):301–8.

3.2

Intergroup T94-0110: Efficacy of Androgen Deprivation Therapy with Radiation Therapy in Locally Advanced Prostate Cancer

	Seven-year overall survival	Seven-year disease-specific survival
Androgen deprivation therapy (n = 602)	66%	79%
Androgen deprivation and radiation therapy (n = 603)	74%	90%
Hazard ratio	0.77	0.57
p-value	0.0331	0.001

Warde PR et al. *Proc ASCO* 2010;**Abstract CRA4504**.

DR LOVE: What about new developments such as proton-beam therapy, abbreviated dosing schedules or stereotactic radiation therapy in localized prostate cancer?

DR ZIETMAN: Proton-beam therapy has been established as an accurate treatment for certain pediatric tumors, such as brain, spine and eye tumors.

The interest in proton-beam therapy for localized prostate cancer has grown substantially in recent years. It offers the theoretical potential for achieving dose escalation and decreasing toxicity.

Few published clinical data support its superiority to alternative forms of conformal radiation therapy for prostate cancer in either efficacy or safety. It will take a trial to demonstrate any superiority, and we are going to start one.

Track 8

DR LOVE: What are your current thoughts about the use of antiandrogen monotherapy compared to LHRH agonists?

DR ZIETMAN: LHRH agonists and high-dose bicalutamide have demonstrated similar efficacy in metastatic disease. Most of the adverse events associated with hormonal therapy, such as affected libido, fatigue, weight gain and bone loss, are less of a problem with antiandrogen therapy than with LHRH agonists. A challenge with agents such as bicalutamide is that men invariably develop gynecomastia (3.3, 3.4). With breast irradiation, the incidence of gynecomastia can be reduced by half, but breast tenderness may remain. ■

3.3 Treatment of Bicalutamide-Induced Breast Events

"The ongoing bicalutamide Early Prostate Cancer (EPC) program has shown that breast events, defined as gynecomastia, breast pain or both, are a significant limitation of bicalutamide. Nearly 90% of patients experienced one or both symptoms and nearly 16% of patients withdrew from the EPC program as a consequence of bicalutamide-induced breast events. Tamoxifen, anastrozole and radiotherapy have all been studied as options for the treatment of breast events. To date, tamoxifen appears to be the superior agent in terms of outcomes; however, further studies are still required to determine the optimal dose and timing of tamoxifen administration for both prophylaxis and treatment."

Sieber PR. *Expert Rev Anticancer Ther* 2007;7(12):1773-9.

3.4 Phase III Trial Comparing the Efficacy of Two Tamoxifen Schedules in Preventing Gynecomastia Induced by Bicalutamide Monotherapy

"Bicalutamide monotherapy is a valuable option for prostate cancer (PCa) patients who wish to avoid the consequences of androgen deprivation; however, this treatment induces gynaecomastia and mastalgia in most patients. Tamoxifen is safe and effective in preventing breast events induced by bicalutamide monotherapy without affecting antitumor activity....

This study demonstrated that tamoxifen 20mg/wk is inferior to tamoxifen 20mg/d in preventing the incidence and severity of bicalutamide-induced breast events. The safety and efficacy of tamoxifen at the common daily dose of 20mg for the prophylaxis of bicalutamide-induced breast events were confirmed."

Bedognetti D et al. *Eur Urol* 2010;57(2):238-45.

SELECT PUBLICATIONS

Warde PR et al. **Intergroup randomized phase III study of androgen deprivation therapy (ADT) plus radiation therapy (RT) in locally advanced prostate cancer (CaP) (NCIC-CTG, SWOG, MRC-UK, INT: T94-0110; NCT00002633).** *Proc ASCO* 2010;**Abstract CRA4504**.

Widmark A et al. **Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): An open randomised phase III trial.** *Lancet* 2009;373(9660):301-8.

INTERVIEW

E David Crawford, MD

Dr Crawford is Professor of Surgery, Urology and Radiation Oncology and Head of the Section of Urologic Oncology at the University of Colorado Health Science Center in Denver, Colorado.

Tracks 1-10

Track 1	Discovery and development of the GnRH agonist leuprolide and the GnRH receptor antagonist degarelix
Track 2	Clinical significance of LHRH agonist-associated tumor flare and testosterone escape levels
Track 3	Rationale for the use of the GnRH receptor antagonist degarelix in clinical practice
Track 4	Impact of incomplete androgen blockade on responses to second-line antiandrogen therapy
Track 5	Efficacy of combined androgen blockade in PCa
Track 6	Use of adjuvant bicalutamide monotherapy in clinical practice
Track 7	Perspective on the current landscape of managing PSA-only PCa
Track 8	Use of hormonal therapy with or without chemotherapy for patients with PSA-only PCa
Track 9	Benefits of earlier treatment with chemotherapy for castration-resistant PCa
Track 10	Emerging treatment options for castration-resistant PCa

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you describe the differences between GnRH agonists and the GnRH antagonist degarelix in prostate cancer?

DR CRAWFORD: GnRH is a decapeptide synthesized in the hypothalamus that traverses to the pituitary gland, where it leads to the pulsatile release of luteinizing hormone (LH) and thereby testosterone. Leuprolide is a GnRH agonist that works by saturating the GnRH receptor, downregulating the LH and eventually reducing testosterone levels. Before the downregulation, the LH level rises and so does the testosterone level, causing a flare reaction before the actual reduction of testosterone.

In contrast, degarelix, a GnRH receptor antagonist, shuts off the GnRH receptor and thus immediately causes a drop in LH and testosterone levels. Degarelix is highly effective in lowering testosterone quickly and maintaining castration levels of testosterone (Klotz 2008; [4.1]). The one drawback is the

need for monthly injections, whereas the current formulations of GnRH agonists can be administered at a frequency as low as once every six months. However, this is the drug we wanted from the beginning, and it does not cause the LHRH agonist-associated flare reaction.

DR LOVE: What is the clinical significance of the flare reaction with GnRH agonists?

DR CRAWFORD: If a patient has symptomatic primary or metastatic disease, then a flare reaction can clearly cause additional pain or urinary problems. The clinical significance for patients with asymptomatic biochemical failure is less clear. However, when testosterone levels rise, then PSA levels also rise. I don't know the clinical significance of this, but I don't believe that it is good.

With a repeat administration of a GnRH agonist, approximately 20 percent of patients can experience a miniflare, with an increase in testosterone and PSA levels, which again may not be good. A relationship is evident between the testosterone escape and the time of development of CRPC (Morote 2009). A testosterone escape greater than 50 ng/dL may lead to a 14-month difference in the time of CRPC development compared to that of patients in whom testosterone is kept below 20 ng/dL.

In addition, it can take up to 80 days before a castration level of testosterone is achieved with an agonist (Klotz 2008). If the goal is to lower the testosterone level, it should be done quickly because the six-month testosterone level has been shown to be prognostic. The difference in survival between people with six-month testosterone levels of less than 20 ng/dL, 20 to 50 ng/dL and greater than 50 ng/dL can reach four to six months (Perachino 2010).

Outside of a clinical trial, I talk to patients about GnRH receptor antagonists and encourage their use, especially for those who need their testosterone levels to be lowered quickly and effectively.

4.1

Phase III, 12-Month Comparative Study of the Effects of Degarelix versus Leuprolide on Testosterone Suppression in Men with Any Stage Prostate Cancer

	Degarelix 240/80 mg	Degarelix 240/160 mg	Leuprolide
% patients with ≤0.5 ng/mL at three days	96.1%	95.5%	0%
% patients with monthly testosterone ≤0.5 ng/mL from day 28 to 364	97.2%	98.3%	96.4%

Klotz L et al. *BJU International* 2008;102(11):1531-8.

Track 5

DR LOVE: What do we know about combined androgen blockade in prostate cancer?

DR CRAWFORD: After castration, low levels of testosterone remain, which may further stimulate prostate cancer. This may be coming from adrenal glands. Combined androgen blockade with GnRH agonists and antiandrogens could potentially block these low levels of testosterone, and the randomized Intergroup study 0036 demonstrated a 7.1-month survival benefit with combined blockade compared to daily leuprolide alone (Crawford 1990).

The urology community has not totally embraced the combined blockade, and the argument offered is that daily leuprolide is not a good drug and flutamide only made it appear better. I believe that adrenal androgen is real, and I administer combined blockade with GnRH agonists and bicalutamide.

With GnRH receptor antagonists such as degarelix, one may not need an antiandrogen. Although degarelix cannot eradicate adrenal androgen, the testosterone levels are low, and I do not use bicalutamide when administering degarelix. GnRH antagonists lead to a rapid reduction in prostate size.

Tracks 9-10

DR LOVE: Do you ever consider using regimens that include chemotherapy for patients with PSA-only CRPC?

DR CRAWFORD: Some Phase II studies have evaluated earlier chemotherapy, but we lack studies of the integration of chemotherapy and hormonal therapy in this setting. I occasionally consider this approach off protocol.

DR LOVE: What about earlier treatment of metastatic CRPC?

DR CRAWFORD: Medical oncologists usually want to wait until the patient experiences symptoms before offering chemotherapy, although a significant subset of patients had minimal or no symptoms in both the SWOG study (Petrylak 2004) and the TAX-327 trial (Tannock 2004). I believe earlier may be better, but the debate continues. ■

SELECT PUBLICATIONS

Crawford ED et al. **Treatment of newly diagnosed state D2 prostate cancer with leuprolide and flutamide or leuprolide alone, phase III, intergroup study 0036.** *J Steroid Biochem Mol Biol* 1990;37(6):961-3.

Klotz L et al. **The efficacy and safety of degarelix: A 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer.** *BJU International* 2008;102(11):1531-8.

Morote J et al. **Individual variations of serum testosterone in patients with prostate cancer receiving androgen deprivation therapy.** *BJU International* 2009;103(3):332-5.

Perachino M et al. **Testosterone levels in patients with metastatic prostate cancer treated with luteinizing hormone-releasing hormone therapy: Prognostic significance?** *BJU International* 2010;105(5):648-51.

Petrylak DP et al. **Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer.** *N Engl J Med* 2004;351(15):1513-20.

Tannock IF et al. **Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer.** *N Engl J Med* 2004;351(15):1502-12.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the IMPACT trial, the vaccine sipuleucel-T resulted in a _____ median improvement in overall survival compared to placebo among patients with asymptomatic or minimally symptomatic, castration-resistant metastatic prostate cancer.**
   a. Two-month
   b. Four-month
   c. 10-month

2. **In the TROPIC trial, the novel taxane cabazitaxel in combination with prednisone demonstrated a significant improvement in _____ compared to mitoxantrone/prednisone for patients with castration-resistant metastatic prostate cancer previously treated with docetaxel.**
   a. Overall survival
   b. Progression-free survival
   c. Both a and b

3. **The Phase III trial RTOG-0521 is evaluating hormonal and radiation therapy with or without _____ for patients with high-risk localized prostate cancer.**
   a. Bevacizumab
   b. Sipuleucel-T
   c. Cabazitaxel
   d. Docetaxel

4. **ZD4054 (zibotentan) is a _____ with potential for the treatment of hormone-resistant prostate cancer.**
   a. Specific endothelin receptor A antagonist
   b. Specific endothelin receptor B antagonist
   c. Dual endothelin receptor A and B antagonist

5. **In their study of ZD4054 for patients with hormone-resistant prostate cancer and bone metastases, James and colleagues reported no statistically significant difference in time to disease progression but an improvement in overall survival.**
   a. True
   b. False

6. **The Phase III CALGB-90401 trial, evaluating docetaxel/prednisone with or without bevacizumab for men with metastatic castration-resistant prostate cancer, reported improvements in progression-free survival, measurable disease response, post-therapy PSA decline and overall survival with the addition of bevacizumab to docetaxel/prednisone.**
   a. True
   b. False

7. **A recently reported Phase III trial demonstrated a 12 percent improvement in 10-year prostate cancer-specific mortality with the addition of radiation therapy to hormonal therapy in men with locally advanced prostate cancer.**
   a. True
   b. False

8. **Which of the following adverse events is less problematic in men with prostate cancer treated with bicalutamide compared to LHRH agonists?**
   a. Fatigue
   b. Weight gain
   c. Bone loss
   d. Impaired libido
   e. All of the above

9. **In a Phase III, 12-month comparative study, degarelix suppressed testosterone levels to ≤0.5 ng/mL at each monthly assessment in _____ percent of men compared to zero percent of men receiving leuprolide.**
   a. More than 95
   b. 50
   c. 10

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Prostate Cancer Update — Issue 1, 2010

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
TROPIC: A Phase III trial of the novel microtubule stabilizer cabazitaxel for advanced, castration-resistant PCa	4 3 2 1	4 3 2 1
Activity and tolerability of the selective endothelin A receptor antagonist ZD4054 (zibotentan), an emerging endocrine agent for the treatment of PCa	4 3 2 1	4 3 2 1
CALGB-90401: Phase III trial results of docetaxel/prednisone with or without bevacizumab in metastatic castration-resistant PCa	4 3 2 1	4 3 2 1
Rationale for and development of the GnRH receptor antagonist degarelix	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:

- Appraise the clinical benefits of adjuvant radiation therapy for patients with locally advanced or high-risk prostate cancer. . . . . 4 3 2 1 N/M N/A
- Apply the results of existing and emerging research on the choice and timing of endocrine therapy alone or with radiation therapy to the care of patients with localized, biochemically recurrent or metastatic prostate cancer. . . . . 4 3 2 1 N/M N/A
- Communicate the benefits and risks of taxane-based chemotherapy regimens to patients with recurrent prostate cancer. . . . . 4 3 2 1 N/M N/A
- Summarize emerging efficacy and safety data with targeted agents in castration-resistant prostate cancer, including anti-angiogenic therapy, microtubule stabilizers, specific endothelin A receptor antagonists, immunomodulatory agents and novel inhibitors of testosterone synthesis or activity. . . . . 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

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 editor for this educational activity

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
A Oliver Sartor, MD	4 3 2 1	4 3 2 1
Nancy A Dawson, MD	4 3 2 1	4 3 2 1
Anthony Zietman, MD	4 3 2 1	4 3 2 1
E David Crawford, MD	4 3 2 1	4 3 2 1
Editor	**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 editor for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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Prostate Cancer™

UPDATE

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