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Prostate Cancer™ UPDATE

Conversations with Urologic Oncology Investigators

Bridging the Gap between Research and Patient Care

EDITOR

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INTERVIEWS

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CME Certified

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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

- Effectively utilize prostate cancer-specific nomograms and risk-assessment tools to estimate prognosis and individualize treatment decisions.
- Identify patients who may benefit from prostate cancer risk-reduction strategies, and discuss the evolving role of PSA measurement as a screening tool.
- Appraise the clinical benefits of adjuvant radiation therapy for patients with pathologically advanced 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 for targeted agents in hormone-refractory prostate cancer, including 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

Judd W Moul, MD

Dr Moul is Professor and Chief of the Division of Urologic Surgery at Duke University Medical Center in Durham, North Carolina.

Tracks 1-12

Track 1 **Case discussion:** A 59-year-old man with Gleason 8 prostate cancer (PCa) who had positive margins after prostatectomy received radiation therapy and hormonal therapy and was lost to follow-up for one year during which his PSA level increased to 11.3 ng/mL

Track 2 Salvage radiation therapy with hormonal therapy for PSA progression

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Track 4 Assessing the probability of PCa-specific mortality

Track 5 Efficacy and quality of life with antiandrogen monotherapy compared to LHRH agonist therapy

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Track 7 **Case discussion:** A 62-year-old man experienced a decline in PSA level from 6.0 ng/mL to 0.7 ng/mL after one year of high-dose bicalutamide

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Track 9 **Case discussion:** An 82-year-old asymptomatic man presents with an isolated urethral sarcoma eight years after brachytherapy and external beam radiation therapy for intermediate-risk PCa

Track 10 **Case discussion:** A 62-year-old man whose PSA level was undetectable after prostatectomy for Gleason 6 PCa underwent salvage external beam radiation therapy two years later upon a rise in PSA level to 0.17 ng/mL

Track 11 Watchful waiting for a patient with biochemical recurrence after "adjuvant" radiation therapy

Track 12 Multidisciplinary care for patients with biochemical recurrence

Select Excerpts from the Interview

Track 5

DR LOVE: What's your perception of the efficacy and the quality of life associated with antiandrogen monotherapy compared to an LHRH agonist?

DR MOUL: For a patient who has prostate cancer with positive bone scan results or obvious metastatic disease on CAT scan, the "board" answer is

that peripheral androgen blockade with bicalutamide 150 milligrams is not as efficacious as an LHRH agonist or orchiectomy, based on some European trials. The difference, however, was not great. The difference in median survival between orchiectomy or an LHRH agonist and peripheral androgen blockade was 42 days (Tyrrell 1998).

For patients with PSA recurrence, however, I don't believe we know. We do know that bicalutamide 150 milligrams is probably as effective as an LHRH agonist for a patient with advanced but nonmetastatic prostate cancer (Iversen 2000; [1.1]). Perhaps for many of these men with PSA recurrence, that's a perfectly acceptable therapy.

I believe that the overall quality of life is better with antiandrogen monotherapy, as long as you do something to avoid gynecomastia and nipple tenderness. Typically, if you prescribe bicalutamide 150 milligrams or even lower-dose oral antiandrogen therapy, such as the combination of finasteride and flutamide, you need to use prophylactic breast irradiation to avoid gynecomastia.

1.1

Combined Analysis of Two Randomized Trials Comparing Bicalutamide 150 Milligrams to Castration* for Patients with Nonmetastatic Locally Advanced Prostate Cancer (Median Follow-Up of 6.3 Years)

Efficacy	Bicalutamide 150 mg (n = 320)	Castration* (n = 160)	Hazard ratio (95% CI)	*p*-value
Median OS	63.5 months	69.9 months	1.05 (0.81-1.36)	0.70
Median TTP	NR	NR	1.20 (0.96-1.51)	0.11
Select adverse events	**Bicalutamide 150 mg (n = 320)**	**Castration* (n = 160)**	**Hazard ratio (95% CI)**	***p*-value**
Gynecomastia	49.4%	4.4%	—	—
Breast pain	40.1%	1.9%	—	—
Hot flashes	13.1%	50.0%	—	—

* Orchiectomy (n = 22) and goserelin (n = 138); CI = confidence interval; OS = overall survival; TTP = time to progression

"In this analysis of patients with prostate cancer, no significant difference was seen in survival or time to progression between those treated with 150 milligrams of bicalutamide monotherapy or castration. Benefits to patients were seen in terms of quality-of-life parameters, ie, sexual interest, physical capacity and tolerability, which make bicalutamide monotherapy an attractive alternative to castration for patients with locally advanced prostate cancer."

SOURCE: Iversen P et al. *J Urol* 2000;164(5):1579-82.

Track 6

DR LOVE: Are there any investigational agents that you believe might reach the clinic in the next few years?

DR MOUL: People are discussing ZD4054, which is an endothelin A receptor antagonist being evaluated in a large, global, Phase III program for hormone-refractory prostate cancer. A Phase II trial of ZD4054 suggested an approximately seven-month overall survival advantage in hormone-refractory disease (James 2008; [1.2]).

Many physicians are also discussing abiraterone, an oral agent that works on the androgen-synthesis pathway (Attard 2008). I like to think of it as a more intense antiandrogen. Perhaps in the next decade we'll have a series of oral agents that are more potent to reduce testosterone levels even further and reduce intraprostatic androgen levels.

1.2

Phase II Randomized Trial of ZD4054 for Patients with Hormone-Refractory Prostate Cancer and Bone Metastases

Efficacy	ZD4054 15 mg (n = 98)	ZD4054 10 mg (n = 107)	Placebo (n = 107)
Time to progression			
Median	3.8 months	4.6 months	3.7 months
Hazard ratio vs placebo	0.94	1.09	—
80% confidence interval	0.78-1.14	0.91-1.31	—
p-value vs placebo	0.702	0.553	—
Overall survival			
Median	23.5 months	24.5 months	17.3 months
Hazard ratio vs placebo	0.65	0.55	—
80% confidence interval	0.49-0.86	0.41-0.73	—
p-value vs placebo	0.052	0.008	—
Select adverse events (all grades)	**ZD4054 15 mg (n = 98)**	**ZD4054 10 mg (n = 107)**	**Placebo (n = 107)**
Peripheral edema	48%	39%	10%
Headache	44%	36%	12%
Nasal congestion	34%	28%	4%

"The primary endpoint of time to progression was not achieved in this study, but an improvement was seen in overall survival in both active treatment arms. ZD4054 was well tolerated."

SOURCE: James ND et al. *Eur Urol* 2008;[Epub ahead of print].

Tracks 7-8

Case 1: A 62-year-old man with PSA recurrence received bicalutamide 150 milligrams per day for one year. He had a good PSA response, with the level decreasing from 6.0 ng/mL to 0.7 ng/mL.

DR MOUL: The question in this case is, what is the best PSA response we can expect to obtain with peripheral androgen blockade? Urologists, obviously,

have been familiar with managing PSA recurrence by traditional hormonal therapy, either LHRH agonists alone or LHRH agonists with an oral antiandrogen. For most cases, they are able to bring the serum PSA down to undetectable levels.

This patient did not want to deal with the side effects associated with traditional hormonal therapy and elected oral therapy alone. He received breast irradiation prior to the initiation of bicalutamide, and he's been receiving this treatment for one year. Are we comfortable or uncomfortable with that PSA level? Should we add something else?

I counseled the patient about trying bicalutamide in divided doses of 50 milligrams three times a day for approximately six to eight weeks, followed by a repeat PSA test at his local urologist's office. The patient was also provided with a prescription for finasteride, five milligrams per day, to add should his PSA level not drop further on the divided doses of bicalutamide. This is off label and, truthfully, I'm flying by the seat of my pants because it's not crystal clear what a good PSA level is with that therapy.

DR LOVE: This is a fascinating dilemma. What do you believe might happen?

DR MOUL: I'm happy with his PSA level being less than one, and I'm not inclined to switch him to traditional hormonal therapy unless we see a significant increase in his PSA level. My guess is that switching to bicalutamide three times a day will have a negligible impact and by the time I see him next, he will have started finasteride.

He will be receiving combined peripheral androgen deprivation with bicalutamide 150 milligrams per day and finasteride five milligrams per day. We'll find out whether we can obtain a more robust PSA response with that combination. ■

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Bañez LL et al. **Combined low-dose flutamide plus finasteride vs low-dose flutamide monotherapy for recurrent prostate cancer: A comparative analysis of two phase II trials with a long-term follow-up.** *BJU Int* 2009;[Epub ahead of print].

Iversen P et al. **Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of follow up.** *J Urol* 2000;164(5):1579-82.

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Tyrrell CJ et al. **A randomised comparison of 'Casodex' (bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer.** *Eur Urol* 1998;33(5):447-56.

Warren R, Liu G. **ZD4054: A specific endothelin A receptor antagonist with promising activity in metastatic castration-resistant prostate cancer.** *Expert Opin Investig Drugs* 2008;17(8):1237-45.

INTERVIEW

Eric A Klein, MD

Dr Klein is Chairman of the Glickman Urological and Kidney Institute at the Cleveland Clinic in Cleveland, Ohio.

Tracks 1-16

Select Excerpts from the Interview

Track 3

DR LOVE: Would you review the results from the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which you led?

DR KLEIN: This was a four-arm trial with more than 35,000 men who were assigned in equal numbers to selenium alone, vitamin E alone, both together

or placebo for up to 12 years. At the second planned interim analysis at seven years, no statistically significant difference in the incidence of prostate cancer was found in any of the four arms (Lippman 2009).

The secondary endpoints included the incidence of other common types of cancer (ie, colorectal, lung). We also evaluated all types of cancer combined and overall survival. We found that neither selenium nor vitamin E alone nor the combination had any meaningful effect on those other endpoints. My conclusion from SELECT is that selenium and vitamin E, in the forms and doses we used, are not beneficial (Lippman 2009).

Track 5

DR LOVE: Can you comment on the recent publication of the Physicians' Health Study evaluating vitamins E and C?

DR KLEIN: It was a parallel study evaluating only vitamin E in the prevention of prostate cancer. It didn't include selenium. The dose of vitamin E was the same as in SELECT, but it was administered every other day for seven or eight years. The Physicians' Health Study found that vitamin E had no effect on prostate cancer incidence (Gaziano 2009) or cardiovascular disease (Sesso 2008).

They also studied vitamin C. Not much compelling evidence had suggested that vitamin C would have any effect on prostate cancer, and it didn't. Some other evidence, however, had suggested that vitamin C might prevent cardiovascular disease or cancer in general, but it did not (Gaziano 2009; Sesso 2008).

Track 6

DR LOVE: Could you review the article you and Matthew Simmons wrote in *Urology* about "combined androgen blockade revisited" (Simmons 2009; [2.1])?

DR KLEIN: More than two decades ago Ferdinand LaBrie suggested the idea that combined androgen blockade would cure prostate cancer. His entire argument was that an LHRH agonist reduces serum testosterone levels markedly but it doesn't completely ablate the androgen in the prostate, and the androgen in the prostate, even in small amounts, could still drive the growth of prostate cancer. This is why he added the antiandrogens.

The biology he suggested is absolutely correct, but the antiandrogens we have simply are not powerful enough to overcome intraprostatic testosterone. We've learned that cancer that grows after prolonged periods of androgen deprivation is exquisitely sensitive to minute amounts of androgens because of the changes in the androgen receptor. This is inappropriately called hormone-refractory disease and should be called castrate-resistant disease because castration refers to eliminating serum testosterone.

A whole new class of agents is being developed and tested that is more potent in suppressing the intraprostatic testosterone. It's my belief that drugs in this class, such as abiraterone, will provide the next major advance in the treatment of metastatic prostate cancer.

Track 7

DR LOVE: Would you discuss the Phase I study with abiraterone that was published in the *Journal of Clinical Oncology* last October?

DR KLEIN: It was the first study to report on the activity of abiraterone, a lyase inhibitor in the androgen-synthesis pathway that works as an antiandrogen within the prostate. Abiraterone had a remarkable response rate for men with castrate-resistant disease, which is the lethal phenotype of prostate cancer. We have a drug for the first time that demonstrates meaningful clinical responses (Attard 2008; [2.2]).

2.1

Combined Androgen Blockade Revisited

"Unfortunately, the duration of response for ADT for the majority of men with metastatic disease averages only 18-24 months, and ultimately the vast majority of these patients recur. This recurrence, commonly referred to as "androgen-independent prostate cancer," is characterized by outgrowth of tumor cells that proliferate, despite androgen suppression. However, the term "androgen-independent" is biologically inaccurate in that these recurrent tumors acquire mutations that make them exquisitely sensitive to minute amounts of intraprostatic androgen (IPA), and make them at least partially susceptible to secondary hormonal treatments. Hence, the term "castration-resistant prostate cancer" (CRPC) is more accurate.

Current evidence supports that both development and sustained growth of CRPC is heavily dependent on androgen receptor (AR) signaling, subserved by variable amounts of AR mutations, amplifications, and ligand promiscuity. These molecular alterations are attractive targets for new therapeutic approaches and have allowed rekindling of the concept of total androgen ablation that combines the goal of maximum reduction and/or blockade of both serum and IPA levels to inhibit tumor growth."

SOURCE: Simmons MN, Klein EA. *Urology* 2009;73(4):697-705.

Track 11

DR LOVE: How would you determine whether a man with a PSA level of 3.5 ng/mL and a normal digital rectal exam result should undergo a prostate biopsy?

DR KLEIN: Ian Thompson and his colleagues developed the Prostate Cancer Prevention Trial (PCPT) risk calculator, which is a fabulous tool. It's based on the data from PCPT, which included men who received placebo and were screened yearly with digital rectal exams and PSA tests for seven years and

then underwent a biopsy, either because of an abnormality or at the end of the trial (Thompson 2006). It is a tool I use in my clinic all the time.

When a man asks whether he needs a biopsy, you can use the risk calculator and enter seven variables that each have a low independent predictive value for finding prostate cancer but together provide us with the best prediction. The variables are age, race, PSA level, family history, digital rectal exam, prior negative biopsy and the use of finasteride (Thompson 2006).

After you enter those numbers, you obtain two results. The first is the likelihood that the individual has any chance of prostate cancer of any grade. You also receive an even more useful figure, the likelihood that the individual has high-grade prostate cancer. This is important in the era in which we recognize that a lot of low-grade cancer is overtreated. ■

2.2

Phase I Trial of Abiraterone for Castration-Resistant Prostate Cancer (CRPC): Antitumor Activity

"Greater than 50% declines in PSA confirmed after 1 month that lasted for more than 3 months from the start of treatment were observed in 12 (57%) of 21 patients with CRPC. ...Five (62%) of eight patients with measurable disease at baseline had confirmed partial responses by RECIST. Radiologic regression of pelvic and paraaortic lymphadenopathy was observed in three patients, and regression of soft-tissue metastasis in the pelvis, lungs, and mediastinum was observed in two patients. ...Eleven patients had pain that required analgesics at baseline, and eight of 11 had symptom improvement that allowed a reduction in dose or cessation of analgesic use."

SOURCE: Attard G et al. *J Clin Oncol* 2008;26(28):4563-71.

SELECT PUBLICATIONS

Antonarakis ES et al. **The natural history of metastatic progression in men with PSA-recurrent prostate cancer (PCa) after radical prostatectomy: 25-year follow-up.** Genitourinary Cancers Symposium 2009;**Abstract 5**.

Attard G et al. **Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven.** *J Clin Oncol* 2008;26(28):4563-71.

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Lippman SM et al. **Effect of selenium and vitamin E on risk of prostate cancer and other cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT).** *JAMA* 2009;301(1):39-51.

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Sesso HD et al. **Vitamins E and C in the prevention of cardiovascular disease in men: The Physicians' Health Study II randomized controlled trial.** *JAMA* 2008;300(18):2123-33.

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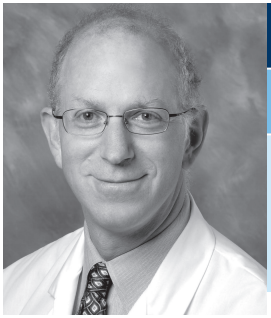

INTERVIEW

Howard Sandler, MD, MS

Dr Sandler is Chairman of the Department of Radiation Oncology at the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center in Los Angeles, California.

Tracks 1-10

Select Excerpts from the Interview

Track 3

DR LOVE: What are the current recommendations for treating locally advanced prostate cancer?

DR SANDLER: In the past, urologists were reluctant to operate on patients with locally advanced disease. As time has passed, however, both the NCCN and the European guidelines have stated that surgery is an option for limited T3 disease, and I agree.

If a surgeon has a reasonable chance of getting around the extracapsular disease and removing the prostate with negative margins, then I believe that's an acceptable choice. If the probability is low that the cancer can be completely removed by surgery, then I believe the patient should be treated with radiation therapy and hormonal therapy.

DR LOVE: When combining hormonal therapy with radiation therapy, do you use complete androgen blockade or an LHRH agonist alone?

DR SANDLER: The studies that have shown a benefit to combining radiation therapy and hormonal therapy have generally used total androgen blockade before and during radiation therapy followed by an LHRH agonist alone for two or three years.

Track 4

DR LOVE: Would you discuss the rationale for and design of RTOG-0521?

DR SANDLER: Until approximately four years ago we had no clear-cut evidence of a life-prolonging cytotoxic therapy for prostate cancer. Then two Phase III trials, TAX-327 and SWOG-S9916, showed a survival advantage with docetaxel in hormone-refractory disease (Petrylak 2004; Tannock 2004). This resulted in a lot of interest in evaluating docetaxel in the adjuvant setting and the development of trials like RTOG-0521.

This trial randomly assigns patients to standard high-dose radiation therapy combined with two years of hormonal therapy with or without six cycles of docetaxel and prednisone (3.1). We hope it will demonstrate that adjuvant chemotherapy is beneficial for prostate cancer. If it does, it will be a landmark event because it will establish the use of chemotherapy as a standard for patients with nonmetastatic disease and will allow us to start exploring more effective adjuvant regimens.

DR LOVE: What has been your experience regarding the tolerability of docetaxel?

DR SANDLER: It is widely used for advanced prostate cancer, and it's reasonably well tolerated. We've accrued more than 400 men to RTOG-0521, and although we've noted some of the toxicities you would expect from docetaxel — neutropenia and thrombocytopenia — we've seen no excessive side effects that one might expect in patients who have recently received pelvic radiation therapy.

DR LOVE: In RTOG-0521, what is the sequence of the treatments?

DR SANDLER: Treatment begins with two months of combined androgen suppression (LHRH agonist and antiandrogen) for downsizing the cancer. Reducing the size of the prostate makes it easier to treat with radiation therapy. We also see a reduction in the number of clonogens, so the radiation therapy has less cancer to kill, and some biologic synergy probably occurs.

Then patients receive radiation therapy while continuing combined androgen suppression. In both arms, once radiation therapy is completed, the LHRH agonist alone is continued for another 20 months. Docetaxel is administered every three weeks for a total of six cycles to half of the patients, beginning four weeks after radiation therapy.

3.1

Phase III Randomized Trial of Androgen Suppression and Radiation Therapy with or without Docetaxel/Prednisone

Protocol IDs: RTOG-0521, NCT00288080
Target Accrual: 600 (Open)

Eligibility

- Localized, high-risk prostate cancer

AS = androgen suppression (LHRH agonist + antiandrogen); 3DCRT = 3D conformal radiation therapy; IMRT = intensity-modulated radiation therapy

Study Contacts

Radiation Therapy Oncology Group

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SOURCES: NCI Physician Data Query, April 2009; Radiation Therapy Oncology Group (RTOG), **www.rtog.org**.

Track 6

DR LOVE: What other trials are evaluating docetaxel for localized prostate cancer?

DR SANDLER: In CALGB-90203, patients are randomly assigned either to proceed directly to radical prostatectomy or to receive chemohormonal therapy (docetaxel in combination with leuprolide acetate or goserelin) followed by surgery (4.1).

The advantage to this approach is that with the biopsy being performed prior to chemotherapy and then the prostate being removed, we'll be able to see, from a biological point of view, what's happening in the prostate. This may allow us to develop assays to predict whether a patient will benefit from chemotherapy in the long run.

Track 8

DR LOVE: Can you comment on the evidence for postprostatectomy radiation therapy for patients with T3N0M0 prostate cancer?

DR SANDLER: Fortunately, Phase III studies evaluating the role of adjuvant radiation therapy in this setting have been published, including the updated report on SWOG-S8794 (Thompson 2009).

SWOG-S8794 demonstrated a statistically significant reduction in distant metastases and an improvement in overall survival for patients who received adjuvant radiation therapy (Thompson 2009; [3.2]). The study seems straightforward, and as a radiation oncologist, I believe the data are clear.

The contrary view is that the study design was not ideal because the patients who did not receive adjuvant radiation therapy had no specific salvage radiation therapy recommended to them. Those who object to adjuvant radiation therapy in these cases believe that patients can be monitored carefully through PSA levels.

If the patient's PSA level becomes detectable, he can be offered radiation therapy at that point, sparing the patients who never demonstrate biochemical failure. ■

3.2

SWOG-S8794: A Randomized Trial of Adjuvant Radiation Therapy (RT) versus Observation for Pathological T3N0M0 Prostate Cancer

	Adjuvant RT (n = 214)	No adjuvant RT (n = 211)	HR (95% CI)	*p*-value
Metastasis-free survival (MFS)				
Events	93	114		
Median MFS	14.7 years	12.9 years	0.71	
10-year estimate	71%	61%	(0.54-0.94)	0.016
Overall survival (OS)				
Deaths	88	110		
Median OS	15.2 years	13.3 years	0.72	
10-year estimate	74%	66%	(0.55-0.96)	0.023

HR = hazard ratio; CI = confidence interval

SOURCE: Thompson IM et al. *J Urol* 2009;181(3):956-62.

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Thompson IM et al. **Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: Long-term follow up of a randomized clinical trial.** *J Urol* 2009;181(3):956-62.

INTERVIEW

Daniel P Petrylak, MD

Dr Petrylak is Associate Professor of Medicine and Director of the Genitourinary Oncology Program at Columbia University Medical Center in New York, New York.

Tracks 1-14

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the randomized crossover study of thalidomide versus placebo for patients with androgen-dependent, PSA-recurrent prostate cancer treated with intermittent androgen ablation?

DR PETRYLAK: This study was designed to determine whether we could use intermittent hormonal therapy and then with thalidomide delay the time

to restarting androgen blockade. All of the patients received six months of induction hormonal therapy, and then they were randomly assigned to receive thalidomide or placebo in the first phase of the trial (Figg 2009).

The patients were monitored, and at the time of PSA progression they stopped treatment with thalidomide or placebo and received another six months of induction hormonal therapy followed by the opposite of what they had received in the first phase. Thus, in the second phase, if they had already received thalidomide, they received placebo, and vice versa (Figg 2009).

Thalidomide definitely delayed disease progression (Figg 2009). This trial is timely considering that two European randomized studies evaluating intermittent hormonal blockade in hormone-sensitive prostate cancer demonstrated survival rates similar to those with continuous combined blockade, with perhaps an improvement in quality of life (Miller 2007; Mottet 2009).

Track 10

DR LOVE: How is docetaxel currently being utilized in clinical practice for the management of metastatic prostate cancer?

DR PETRYLAK: Approximately 60 percent of patients receive docetaxel at some point in their course of castration-resistant disease. That number has been constant since the drug was approved in 2004.

It would be interesting to know the reasons why the other 40 percent have not received docetaxel. It may be that the patient refused treatment, was not referred or simply was not medically fit to receive docetaxel-based therapy.

I've treated patients of all ages with docetaxel. We've seen some patients with good responses and others who experience disease progression while receiving it. The second-generation studies, including bevacizumab, VEGF-trap or atrasentan (SWOG-S0421) are crucial to determining whether we can improve the overall response rate of docetaxel.

Tracks 11-12

DR LOVE: Would you discuss some of the ongoing trials evaluating docetaxel for earlier-stage prostate cancer?

DR PETRYLAK: CALGB-90203 (4.1) randomly assigns patients with high-risk disease to immediate prostatectomy or neoadjuvant docetaxel with an LHRH agonist prior to prostatectomy. Memorial Sloan-Kettering has a randomized Phase III trial, 07-101, evaluating androgen deprivation with or without docetaxel for clinically asymptomatic patients with a rapid PSA doubling time after definitive local therapy for prostate cancer.

ECOG-E3805 is evaluating whether early chemotherapy can increase the time to clinical disease progression compared to hormonal therapy alone for

patients with extensive metastatic disease. In this Phase III trial, patients are randomly assigned to receive androgen deprivation therapy with or without docetaxel.

DR LOVE: How important is the sequencing of chemotherapy and hormonal therapy?

DR PETRYLAK: Arif Hussain has studied sequence in his mouse model in the laboratory. He found that the mice who received docetaxel prior to hormonal therapy tended to live longer than those who received both treatments concomitantly or docetaxel after hormone failure. We may learn that the sequence of treatments is indeed important, as it is in breast cancer (Tang 2006). ■

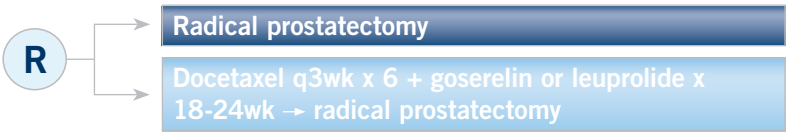
4.1

Phase III Randomized Trial of Radical Prostatectomy with versus without Neoadjuvant Chemohormonal Therapy for High-Risk, Clinically Localized Prostate Cancer

Protocol IDs: CALGB-90203, NCT00430183; Target Accrual: 750 (Open)

Eligibility

- Stage T1 to 3a, high-risk prostate cancer



Study Contacts

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NCIC-Clinical Trials Group
Martin Gleave, MD, Protocol Chair
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SOURCE: NCI Physician Data Query, April 2008.

SELECT PUBLICATIONS

Figg WD et al. **A double-blind randomized crossover study of oral thalidomide versus placebo for androgen dependent prostate cancer treated with intermittent androgen ablation.** *J Urol* 2009;181(3):1104-13.

Hussain M et al. **Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: Data from Southwest Oncology Group trial 9346 (INT-0162).** *J Clin Oncol* 2006;24(24):3984-90.

Miller K et al. **Randomised prospective study of intermittent versus continuous androgen suppression in advanced prostate cancer.** *Proc ASCO* 2007;**Abstract 5015**.

Mottet N et al. **Intermittent versus continuous maximal androgen blockade in metastatic prostate cancer patients. A randomized trial.** Genitourinary Cancers Symposium 2009;**Abstract 171**.

Tang Y et al. **Docetaxel followed by castration improves outcomes in LNCaP prostate cancer-bearing severe combined immunodeficient mice.** *Clin Cancer Res* 2006;12(1):169-74.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Published clinical trial results have demonstrated that antiandrogen monotherapy is comparable in efficacy to castration (LHRH agonist or orchiectomy) for patients with _____.**
   a. A PSA recurrence
   b. Prostate cancer with bone metastases
   c. Prostate cancer (T3/T4) without bone metastases
   d. All of the above

2. **Which of the following is an endothelin A receptor antagonist?**
   a. Abiraterone
   b. ZD4054
   c. Both a and b
   d. None of the above

3. **Which of the following inhibits the androgen-synthesis pathway?**
   a. Abiraterone
   b. ZD4054
   c. Both a and b
   d. None of the above

4. **Which of the following has been shown to prevent prostate cancer?**
   a. Vitamin E
   b. Vitamin C
   c. Selenium
   d. Both a and c
   e. None of the above

5. **The Prostate Cancer Prevention Trial risk calculator uses which of the following variables to determine the risk of finding prostate cancer on biopsy?**
   a. Age
   b. Race
   c. PSA level
   d. Family history
   e. All of the above

6. **Which chemotherapy agent has been found to prolong survival among men with hormone-refractory metastatic prostate cancer?**
   a. Mitoxantrone
   b. Docetaxel
   c. Both a and b
   d. None of the above

7. **Adjuvant docetaxel is currently being evaluated for patients with high-risk, localized prostate cancer.**
   a. True
   b. False

8. **In SWOG-S8794, an _____ was demonstrated among patients who received adjuvant radiation therapy for pathological T3N0M0 prostate cancer compared to those who were observed.**
   a. Improvement in metastasis-free survival
   b. Improvement in overall survival
   c. Both a and b
   d. None of the above

9. **In a preclinical study, Arif Hussain found that mice treated with docetaxel and hormone therapy tended to live longer when the therapies were administered in which sequence?**
   a. Docetaxel administered prior to hormone therapy
   b. Concurrent docetaxel and hormone therapy
   c. Docetaxel administered after hormone failure

10. **What was the improvement in overall survival for patients with hormone-refractory prostate cancer who were treated with ZD4054 compared to placebo?**
    a. Two months
    b. Seven months
    c. No difference was observed

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Prostate Cancer Update — 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
Adjuvant radiation therapy for patients with T3N0M0 PCa	4 3 2 1	4 3 2 1
Postprostatectomy nomogram for 15-year PCa-specific mortality	4 3 2 1	4 3 2 1
RTOG-0521: AS and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by docetaxel and prednisone for high-risk, localized PCa	4 3 2 1	4 3 2 1
CALGB-90203: Neoadjuvant docetaxel and androgen deprivation prior to radical prostatectomy versus immediate radical prostatectomy in high-risk, localized PCa	4 3 2 1	4 3 2 1
Novel agents ZD4054 and abiraterone under investigation in PCa	4 3 2 1	4 3 2 1
Rationale for the investigation of the IMiDs® thalidomide and lenalidomide in PCa	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 (LO) 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:

- Effectively utilize prostate cancer-specific nomograms and risk-assessment tools to estimate prognosis and individualize treatment decisions . . . . . 4 3 2 1 N/M N/A
- Identify patients who may benefit from prostate cancer risk-reduction strategies, and discuss the evolving role of PSA measurement as a screening tool. . . . . 4 3 2 1 N/M N/A
- Appraise the clinical benefits of adjuvant radiation therapy for patients with pathologically advanced 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 for targeted agents in hormone-refractory prostate cancer, including 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

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

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
Judd W Moul, MD	4 3 2 1	4 3 2 1
Eric A Klein, MD	4 3 2 1	4 3 2 1
Howard Sandler, MD, MS	4 3 2 1	4 3 2 1
Daniel P Petrylak, 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

Name: ..... Specialty: .....

Professional Designation:

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Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: ..... Date: .....

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at CME.ResearchToPractice.com.

PCU109

Prostate Cancer™ UPDATE

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Prostate Cancer™

UPDATE

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