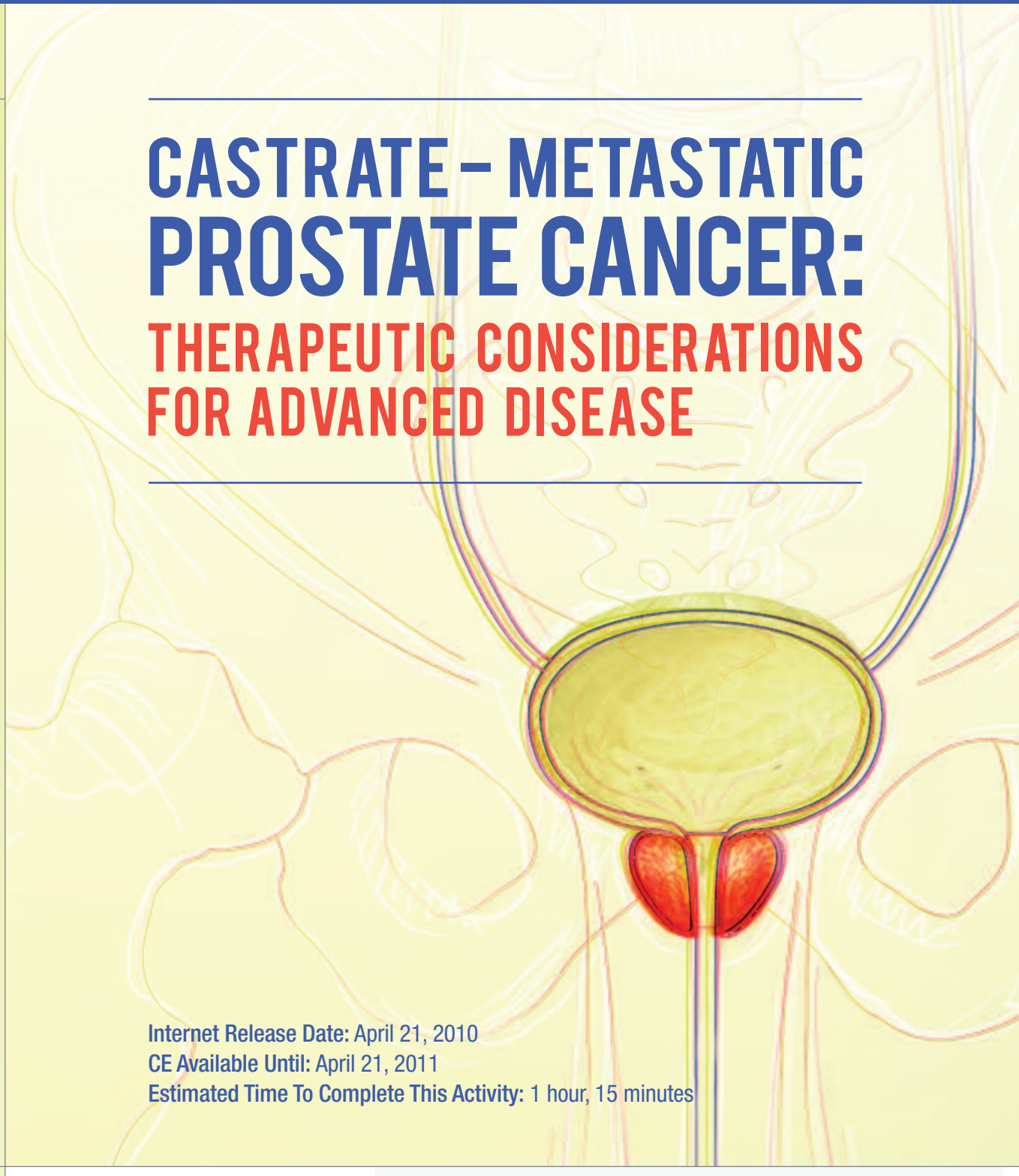
WORKBOOK

VIRTUAL LECTURE & PODCAST

CASTRATE–METASTATIC PROSTATE CANCER:

THERAPEUTIC CONSIDERATIONS FOR ADVANCED DISEASE



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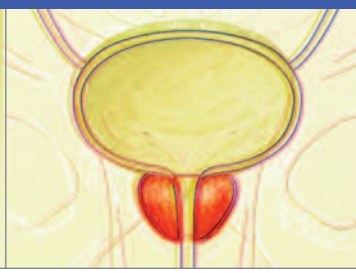

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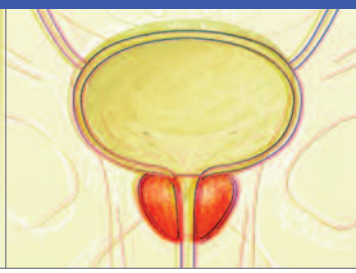
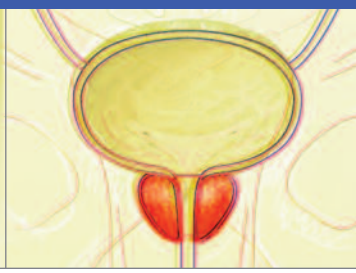


WELCOME & INTRODUCTION	**Sherri Kramer, MD** *Director*, Medical Affairs, RMEI
CASTRATE-METASTATIC PROSTATE CANCER: **THERAPEUTIC CONSIDERATIONS FOR ADVANCED DISEASE**	**Robert Dreicer, MD, MS, FACP** *Chairman*, Department of Solid Tumor Oncology Taussig Cancer Institute *Professor of Medicine* Cleveland Clinic Lerner College of Medicine Cleveland, Ohio
QUESTION-AND-ANSWER SESSION	Facilitated by **Sherri Kramer, MD** Questions answered by **Robert Dreicer, MD, MS, FACP**
WRAP-UP & CONCLUSION	**Sherri Kramer, MD**

OVERVIEW



TARGET AUDIENCE

This activity has been designed to meet the educational needs of physicians, pharmacists, and registered nurses who specialize in the care of patients with prostate cancer.

ACTIVITY PURPOSE

This activity is intended to provide healthcare professionals with clinical information that will contribute to improving competence in the treatment or management of patients with castrate-refractory prostate cancer (CRPC).

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be better able to:

- Outline clinical criteria for the classification of castrate-metastatic prostate cancer (CMPC)
- Describe therapeutic options for patients with progressive CMPC
- Summarize data for emerging therapies in CMPC
- Apply clinical evidence for best treatment strategies in CMPC to improve patient care

STATEMENT OF NEED

Castrate-refractory prostate cancer (CRPC), which is characterized by tumor progression despite castrate levels of testosterone, develops in nearly all prostate cancer patients who are treated with androgen-deprivation therapy. Recent research has suggested that androgen receptor expression is important for regulation of tumor growth, reflecting a shift away from the widely held belief that CRPC is androgen-independent.[1] While researchers contemplate the implications of these new findings, healthcare professionals are faced with the challenge of tailoring therapy to individual patients. When choosing between second-line hormonal therapy and chemotherapy, physicians need to consider serum markers, patient age and pre-existing comorbidities, and toxic late effects of therapy that may affect outcomes and patient quality of life.[2,3] Patients with aggressive disease may benefit from investigational strategies, but the current body of literature lacks consensus for directing such treatment decisions.[3] As such, healthcare professionals who treat patients with CRPC would benefit from educational activities that outline optimal methods of defining, assessing, and treating this condition.

[1]Mohler JL. *Adv Exp Med Biol.* 2008;617:223-234.

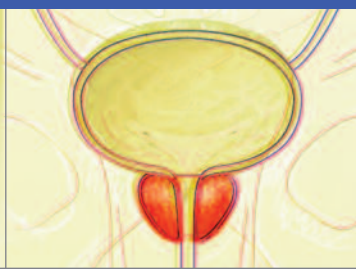
[2]Hall WH, et al. *Prostate Cancer Prostatic Dis.* 2005;8:22-30.

[3]Shepard DR, Raghavan D. *Nat Rev Clin Oncol.* 2010;7(1):13-21.

STATEMENT OF SUPPORT

This activity is jointly sponsored by Robert Michael Educational Institute LLC and Postgraduate Institute for Medicine, and is supported by educational grants from sanofi-aventis and Genentech.

FACULTY BIOGRAPHY



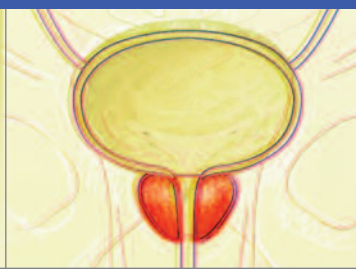
ROBERT DREICER, MD, MS, FACP

Chairman, Department of Solid Tumor Oncology
Taussig Cancer Institute
Cleveland Clinic
Professor of Medicine
Cleveland Clinic Lerner College of Medicine
Cleveland, Ohio

Robert Dreicer, MD, MS, FACP, is chairman of the Department of Solid Tumor Oncology at the Cleveland Clinic and a professor of medicine at the Cleveland Clinic Lerner College of Medicine. After receiving master of science (tumor biology) and medical degrees from the University of Texas in Houston, Dr. Driecer went on to complete residency training in internal medicine at Indiana University in Indianapolis. He then obtained a medical oncology fellowship at the University of Wisconsin Clinical Cancer Center in Madison, Wisconsin. A fellow of the American College of Physicians, Dr. Dreicer is also board-certified in internal medicine and medical oncology.

Dr. Dreicer's primary research interests focus on the management of genitourinary malignancies, and he is principal investigator of several ongoing studies in this area. His research findings have been widely published, and he is currently an associate editor of *Urology* and a member of the editorial boards of the *Journal of Clinical Oncology, New England Journal of Medicine's Journal Watch Hematology/Oncology*, and *The Journal of Supportive Oncology*. In addition to serving as chair of the Bladder Subcommittee of the Eastern Cooperative Oncology Group, Dr. Dreicer has held leadership roles with the US Department of Defense Prostate Cancer Integration Panel and the steering committee of the America Society of Clinical Oncology's 2008 Genitourinary Oncology Meeting.

ACCREDITATION AND CREDIT



PHYSICIAN CONTINUING EDUCATION

ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Robert Michael Educational Institute LLC (RMEI) and Postgraduate Institute for Medicine (PIM). PIM is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION

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ACCREDITATION STATEMENT

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CREDIT DESIGNATION

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If you have received credit for UAN 0809-9999-10-082-L01-P, you are not eligible for this activity.

TYPE OF ACTIVITY: Knowledge

NURSING CONTINUING EDUCATION

CREDIT DESIGNATION

This educational activity for 1.2 contact hours is provided by Postgraduate Institute for Medicine.

ACCREDITATION STATEMENT

Postgraduate Institute for Medicine is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

CALIFORNIA BOARD OF REGISTERED NURSING

Postgraduate Institute for Medicine is approved by the California Board of Registered Nursing, Provider Number 13485 for 1.5 contact hours.

A statement of credit will be issued only upon receipt of a completed activity evaluation form and will be mailed to you within 4 weeks.

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There is no fee for this educational activity.

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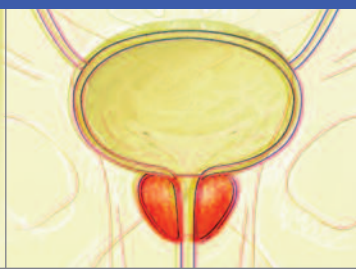

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The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CE activity:

- **Robert Dreicer, MD, MS, FACP**, has affiliations with Ortho-McNeil, Endo Pharmaceuticals, Celgene Corporation, Astra-Zeneca *(Consultant)*; Millennium Pharmaceuticals, Inc. *(Research, Consulting)*; Eli Lilly and Company *(Research)*; and sanofi-aventis *(Honoraria)*.

The ***planners and managers*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CE activity:

ROBERT MICHAEL EDUCATIONAL INSTITUTE LLC

- **Sherri Kramer, MD**, has no affiliations with commercial interests to disclose.
- **Laura Altobelli, MS**, has no affiliations with commercial interests to disclose.

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- **Jan Hixon, RN, BSN, MA**, has no affiliations with commercial interests to disclose.
- **Trace Hutchison, PharmD**, has no affiliations with commercial interests to disclose.
- **Julia Kirkwood, RN, BSN**, has no affiliations with commercial interests to disclose.
- **Jan Schultz, RN, MSN, CCMEP**, has no affiliations with commercial interests to disclose.

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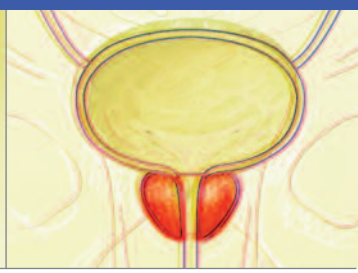
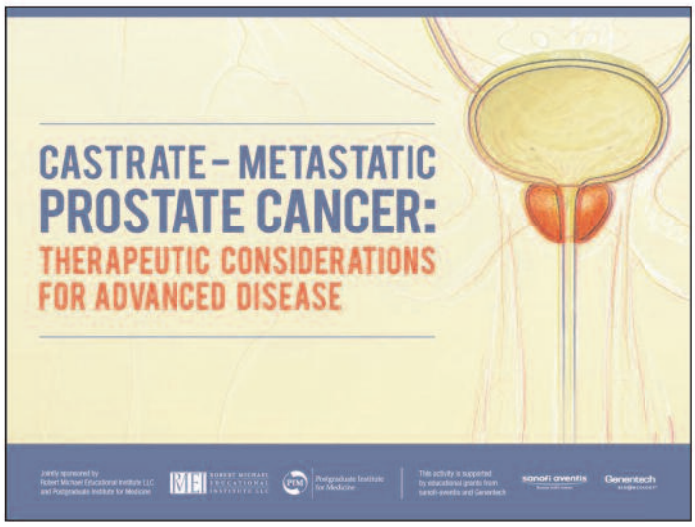
DISCLAIMER

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

PRESENTATION





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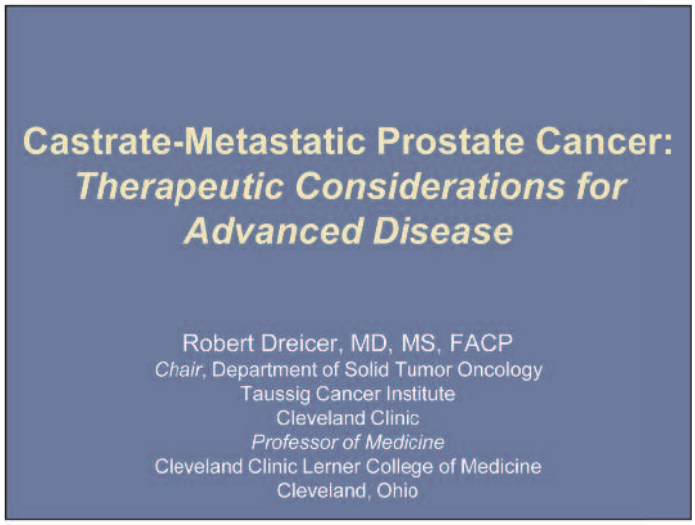

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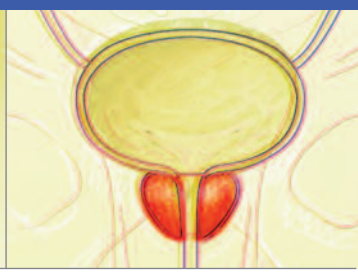
PRESENTATION



Disclosure of Conflicts of Interest

Robert Dreicer, MD, MS, FACP

Dr. Robert Dreicer has affiliations with Ortho-McNeil, Endo Pharmaceuticals, Celgene Corporation, Astra-Zeneca (*Consultant*); Millennium Pharmaceuticals, Inc. (*Research*, *Consulting*); Eli Lilly and Company (*Research*); and sanofi-aventis (*Honoraria*).

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Learning Objectives

- Outline clinical criteria for the classification of castrate-metastatic prostate cancer (CMPC)
- Describe therapeutic options for patients with progressive CMPC
- Summarize data for emerging therapies in CMPC
- Apply clinical evidence for best treatment strategies in CMPC to improve patient care

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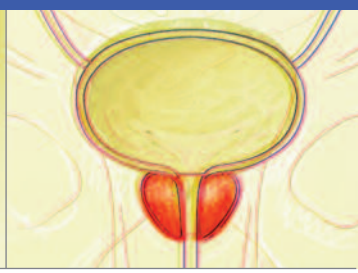
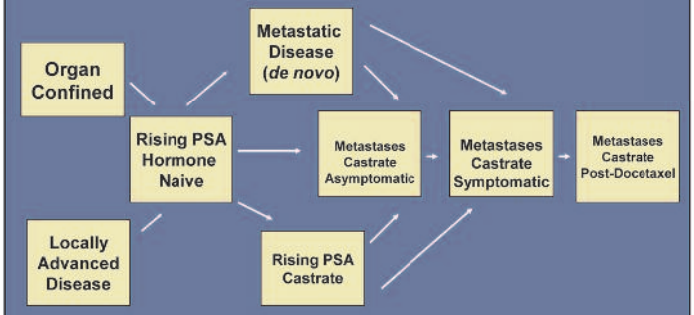


Clinical States in Prostate Cancer



PSA=prostate-specific antigen.
Adapted from Scher HI, et al. *J Clin Oncol*. 2008;26:1148-1159; with permission.

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Castrate-Metastatic Prostate Cancer: YES Hormone Refractory/Androgen Independent (HR/AI) Prostate Cancer: NO

- Historical paradigm: HR/AI prostate cancer
  - Patient receives androgen deprivation therapy (ADT) for metastatic disease
  - Early evidence of "resistance" typically manifests as rising PSA or progression of symptoms with radiographic findings on imaging
  - Serum testosterone less than 50 ng/dL
- At time of disease progression, management typically consisted of maintaining castrate levels of testosterone, although there was limited evidence to support this practice

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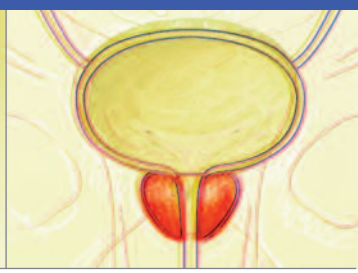
PRESENTATION



Castrate-Metastatic Prostate Cancer: YES Hormone Refractory/Androgen Independent (HR/AI) Prostate Cancer: NO

- Ample evidence of "secondary" hormonal therapy agents (antiandrogens/ketoconaozle/estrogens) result in clinical response despite patients being "REFRACTORY" to hormonal therapy
- Are these patients really hormone refractory/ androgen independent?

7

Androgen Receptor as a Therapeutic Target

- Intraprostatic (*in situ* and metastatic) levels of dihydrotestosterone (DHT) and testosterone have been shown to remain elevated despite castrate serum levels
- Androgen receptor (AR) signaling pathways have also been shown to be persistently activated
- Emergence of a hypersensitive phenotype (likely though AR mutation, amplification, and/or AR modulation by signaling pathways) renders these cells exquisitely sensitive to extremely low levels of exogenous androgens

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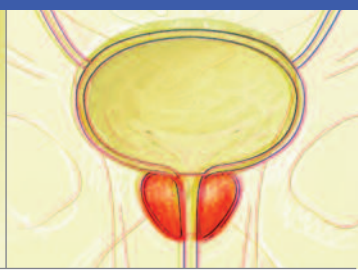

Androgen Receptor as a Therapeutic Target

- AR signaling is a key factor in prostate cancer growth despite castrate serum levels of testosterone
- Newer and more effective methods of blocking androgen synthesis and/or AR antagonists may have promise as therapeutic agents

9

Therapeutic Considerations in the Management of Patients With CMPC

- Biochemical vs clinical/radiographic progression
- Symptomatic vs asymptomatic

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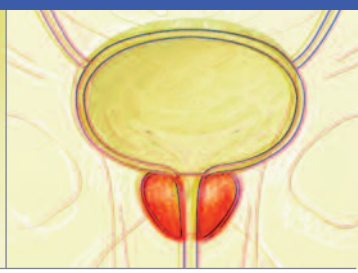
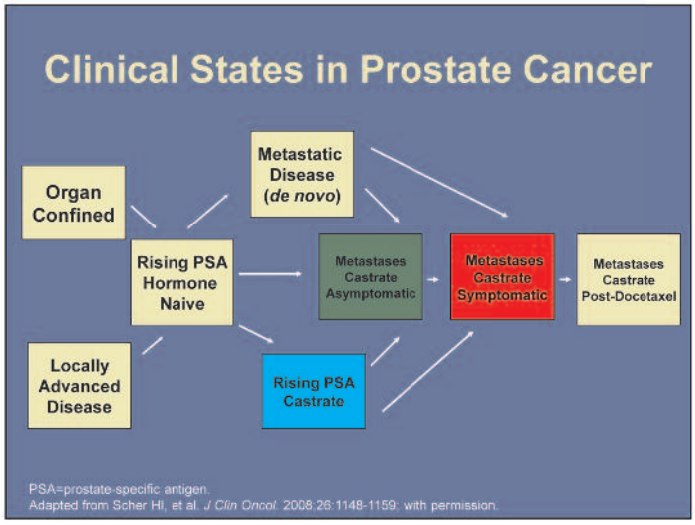
PRESENTATION





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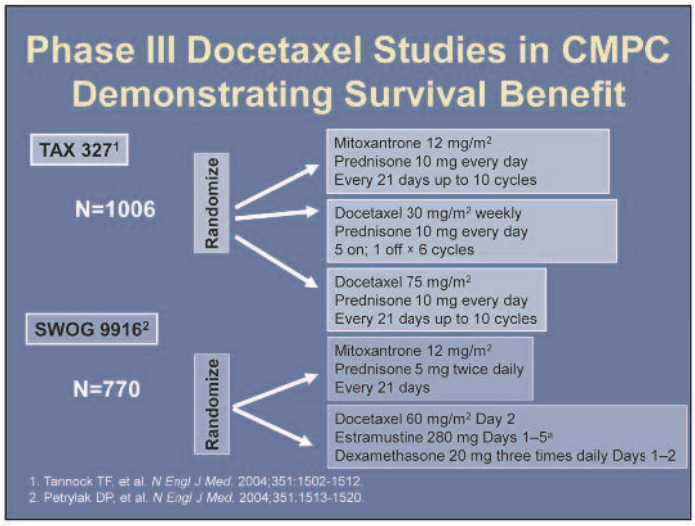

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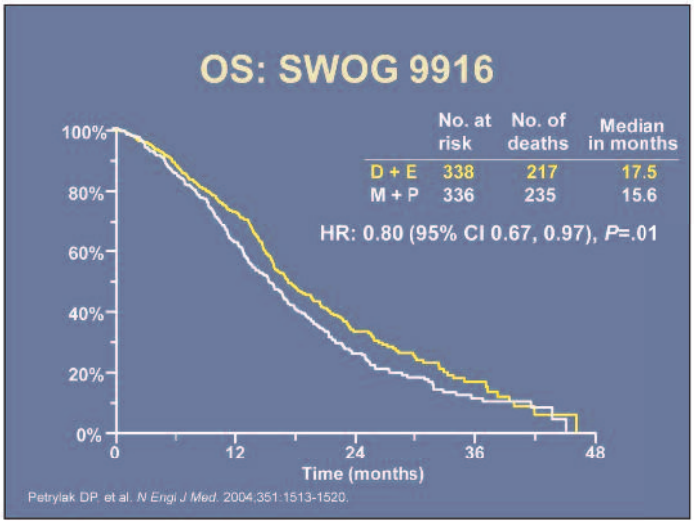

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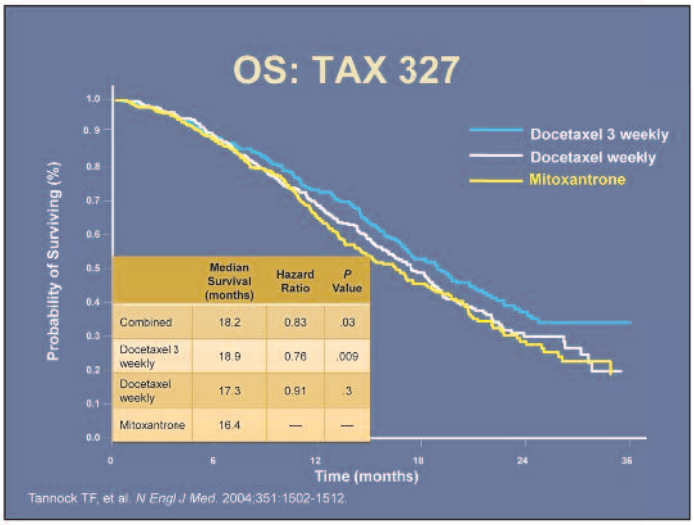

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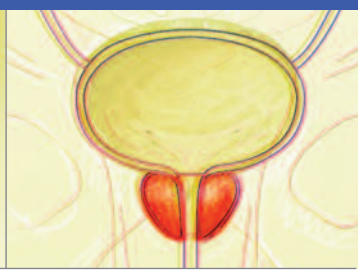

Docetaxel-Based Therapy: Observations From Long-Term Follow-Up

- After 5 years of follow-up, 867 deaths have occurred (initial study results based upon 557 deaths)
- Median survival in the D3P group is now 19.2 months, compared with 17.8 months for the D1P group and 16.3 months for the M+P group
- The difference in survival between the D3P and the M+P groups remains highly significant (*P*=.004)
- **The percentages of patients who remained alive for >3 years were 18.6%, 16.8%, and 13.5%, respectively, in the D3P, D1P, and M+P groups**

Berthold DR, et al. *J Clin Oncol*. 2008;26:242-245.

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Relationships Among PSA Levels, Pain, Quality of Life Response, and Survival in TAX 327

- Men with minimal symptoms had prolonged survival compared with all participants, but this does not necessarily imply benefit from early use of chemotherapy
- Neither PSA nor pain response can substitute for overall survival as a primary endpoint in future phase III studies

Berthold DR, et al. *Clin Cancer Res*. 2008;14:2763-2767.

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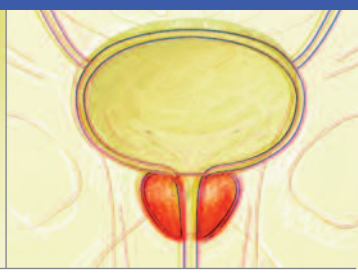

Management Issues: Patients With Asymptomatic CMPC

- Goals of therapy
- Therapeutic metaphysics
  - Symptomatic patients derive "dual" benefit
  - Role of docetaxel-based investigational therapy
  - Recognition of role/utility of drug holiday and retreatment

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Emerging Therapeutics in Patients With CMPC

- AR-targeted therapies
  - Abiraterone**
  - MDV3100*
- Immunomodulatory
  - Sipuleucel T***
  - Lenalidomide*
- Cytotoxics
  - Cabazitaxel**
- Antiangiogenic targeted therapies
  - Bevacizumab**
  - Sunitinib*
- Bone-targeted therapies
  - Denosumab**
  - ZD 4054 (endothelin A inhibitor)*

* Phase III trial underway
** Phase III trial completed
*** Phase III trial reported

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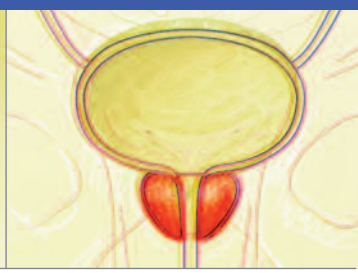

Abiraterone

- Abiraterone acetate is an inhibitor of the CYP 17 (17α-hydroxylase and $C_{17,20}$-lyase) dual enzyme complex, which is principally responsible for androgen synthesis

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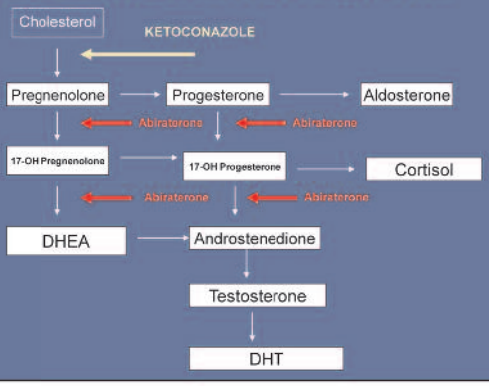
Steroid Pathway: Impact of Ketoconazole/Abiraterone



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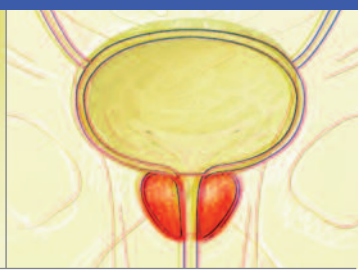

Phase II Trials of Abiraterone Acetate in Castration-Resistant Prostate Cancer (CRPC)

Patient Population	n	PSA Decline ≥50%	Tumor Response (RECIST)	ECOG PS Improvement (At Least One Level)
CRPC: Chemotherapy naïve[1]	33	24 (73%)	PR: 9 (27%) SD: 19 (58%)	8 (61.5%)
CRPC: Prior docetaxel[2]	47	24 (51%)	PR: 6 (13%) SD: 25 (53%)	11 (35%)
CRPC: Prior docetaxel[3]			(n = 18)	
No prior ketoconazole	31	16 (52%)	PR: 3 (17%)	16 (48%)
Prior ketoconazole	27	8 (30%)	SD: 11 (61%)	

1. Ryan C, et al. *J Clin Oncol*. 2009;27(suppl):245s (abstract 5046).
2. Reid AH, et al. *J Clin Oncol*. 2009;27(suppl):246s (abstract 5047).
3. Danila DC, et al. *J Clin Oncol*. 2009;27(suppl):246s (abstract 5048).

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Development of a Second-Generation Antiandrogen for Treatment of Advanced Prostate Cancer (MDV3100)

- Small molecule AR antagonist
- MDV3100 binds the AR with greater relative affinity than the clinically used antiandrogen bicalutamide
- Reduces the efficiency of its nuclear translocation and impairs both DNA binding to androgen response elements and recruitment of coactivators
- Orally available
- Induces tumor regression in mouse models of castration-resistant (bicalutamide resistant) human prostate cancer

Tran C, et al. *Science*. 2009;324:787-790.

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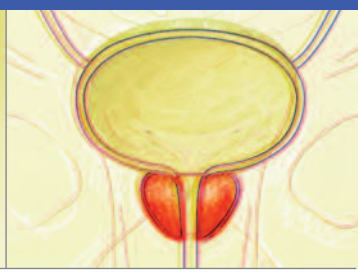
PRESENTATION



Phase I/II Study of MDV3100 in CRPC: Efficacy

	Chemotherapy Naïve (n=65)	Post-Chemotherapy (n=75)
50% decline in PSA	62%	51%
Soft tissue (best response)	n=25	n=34
Partial response	36%	12%
Stable disease	44%	53%
Bone scan (week 12)	n=41	n=68
Stable disease	63%	51%
Time to PSA progression	NR	186 days
Time to radiographic progression	NR	201 days

- Circulating tumor cell (CTC) conversion rates from unfavorable to favorable status, and position emission tomography scan correlated with MDV3100 activity
- Phase III placebo-controlled trial of MDV3100 at 240 mg/d in patients with docetaxel-pretreated CRPC just opened
  - 25% overall survival improvement (12 to 15 months); sample size 1170 (3:1), 85% power; $P = .05$, two-sided; CTCs and profiling as correlative studies

Scher HI, et al. *J Clin Oncol*. 2009;27(Suppl):15s (abstract 5011).

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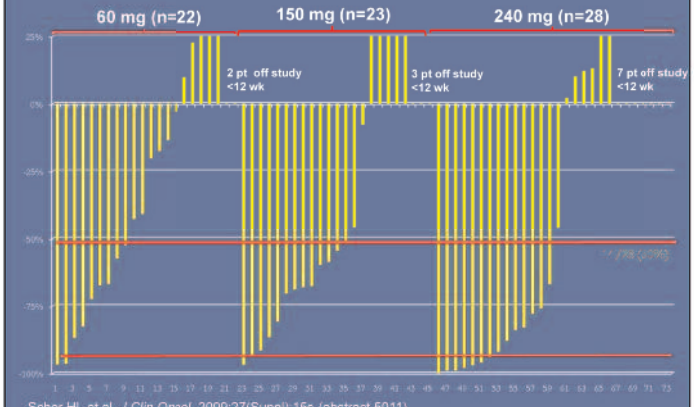
Percent PSA Change From Baseline at 12 Weeks for Patients & Dose Response (N=73)



Scher HI, et al. *J Clin Oncol*. 2009;27(Suppl):15s (abstract 5011).

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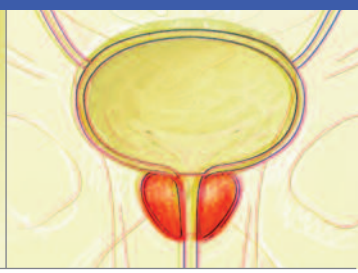
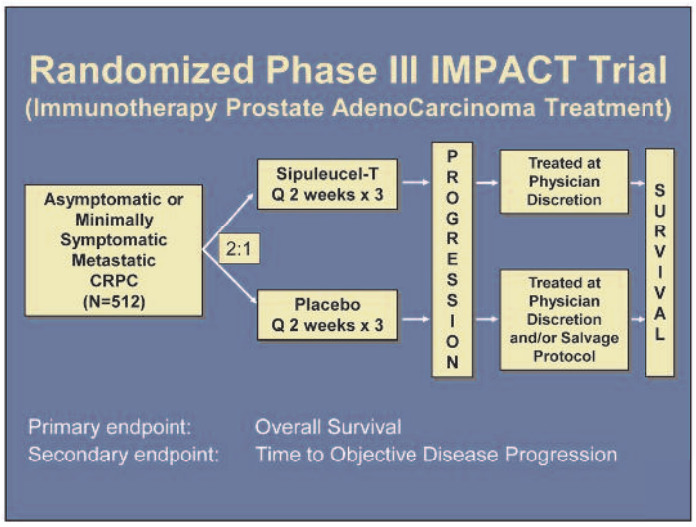
PRESENTATION





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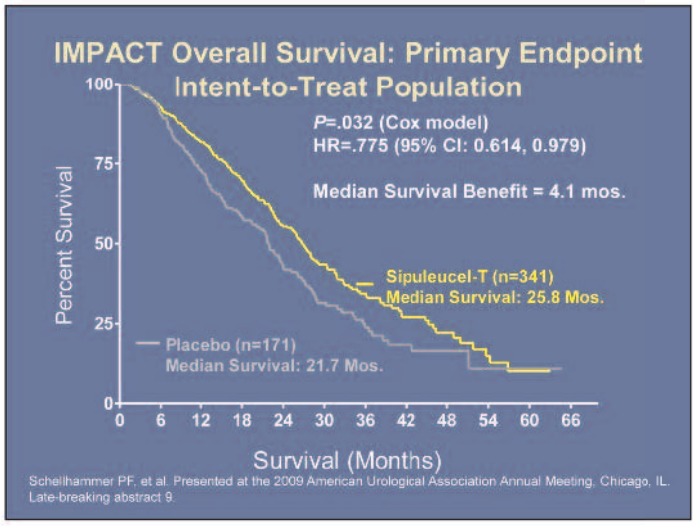

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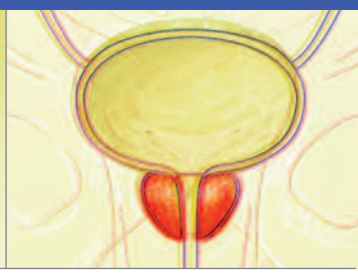

CALGB 90401: Randomized Double-Blinded Placebo-Controlled Phase III Trial Comparing Docetaxel + Prednisone With or Without Bevacizumab in Men With HRPC

Eligibility
Metastatic PC
T <50 ng/mL
No prior chemo
Adequate hem, renal, and liver function

→ **Stratification**
Halabi nomogram

→ RANDOMIZE

→ Docetaxel Q 3 wks + Prednisone + Placebo

→ Docetaxel Q 3 wks + Bevacizumab + Prednisone

N=1020 patients
CALGB, ECOG, NCIC

27

TROPIC: Phase III Registration Study

mCRPC patients who progressed during and after treatment with a docetaxel-based regimen (N=755)

↓

Stratification factors
ECOG PS (0, 1 vs. 2) • Measurable vs. non-measurable disease

↓

- cabazitaxel 25 mg/m² q 3 wk + prednisone* for 10 cycles (n=378)
- mitoxantrone 12 mg/m² q 3 wk + prednisone* for 10 cycles (n=377)

*Oral prednisone/prednisolone: 10 mg daily

Primary endpoint: OS
Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression

Sartor AO, et al. ASCO GU Symposium abstr 9, 2010.

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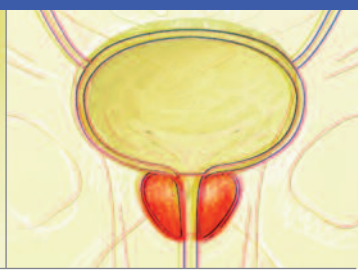
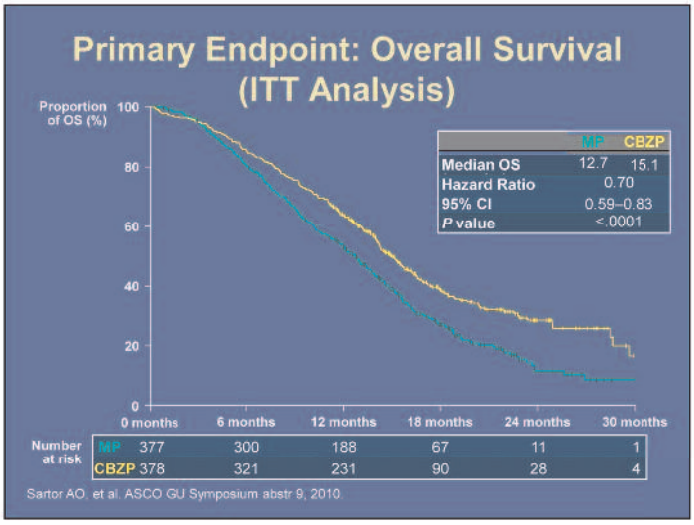
PRESENTATION





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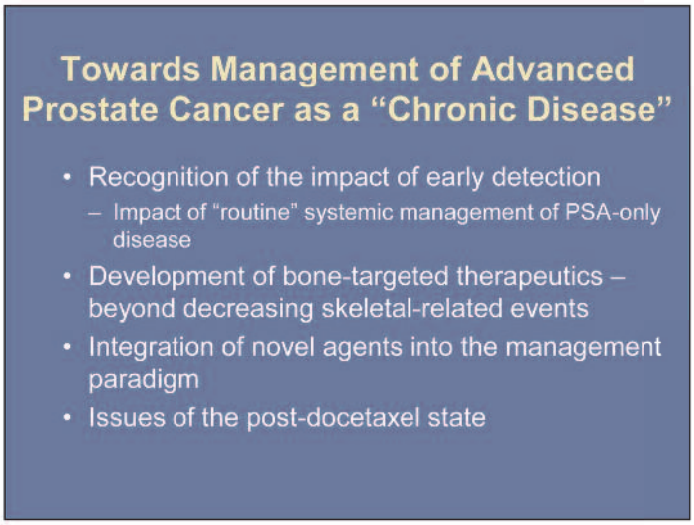

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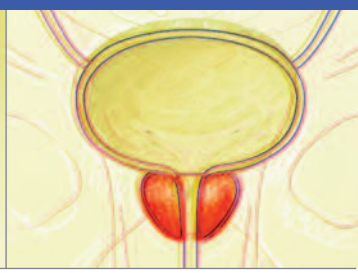

Question-and-Answer

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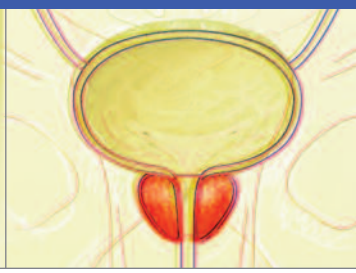
REFERENCES



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