

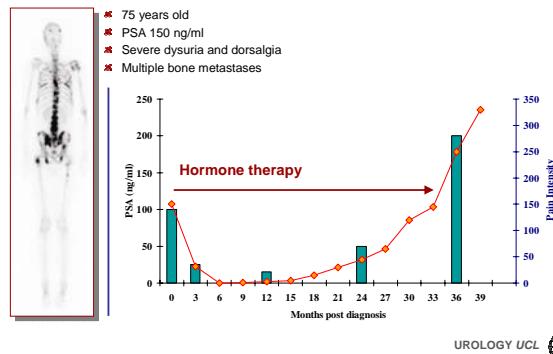
## New developments in the treatment of hormone-refractory prostate cancer (HRPC)

Bertrand TOMBAL, MD, Ph.D  
Service d'Urologie  
UCL Saint Luc



CLINIQUES UNIVERSITAIRES SAINT-LUC

## Patients yesterday



## Patients today



- 58 years old
- Active lifestyle
- PSA 8 ng/ml
- 2 (+) Bx - Gleason 7
- Wants to live long and well

### Radical prostatectomy

### Radiotherapy

### Metastases

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## Hormone resistance today

- Non Metastatic locally advanced
- PSA recurrence after local treatment

PSA (ng/ml)

Hormone therapy

### Non-metastatic PSA increasing

### Metastatic Asymptomatic

### Symptoms

Metastases

PSA recurrence

Metastases

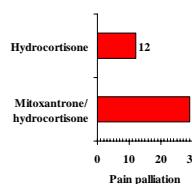
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## Chemotherapy : docetaxel and beyond

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## Palliative chemotherapy

### Mitoxantrone/prednisone vs. prednisone in patients with symptomatic HRPC (n=161)



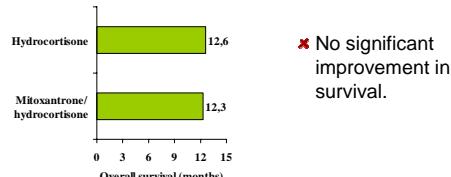
- Primary endpoint: palliative pain response
- Duration of palliation: 43 weeks vs. 18 weeks
- No difference in PSA or survival

Tannock et al. J Clin Oncol 1996;14:1756-1764

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## Palliative chemotherapy

### Mitoxantrone/prednisone vs. prednisone in patients with symptomatic HRPC (n=161)

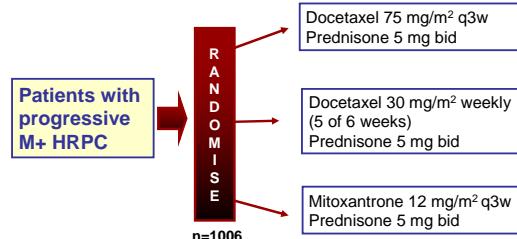


Kantoff et al. J Clin Oncol 1999;17:2506-2513

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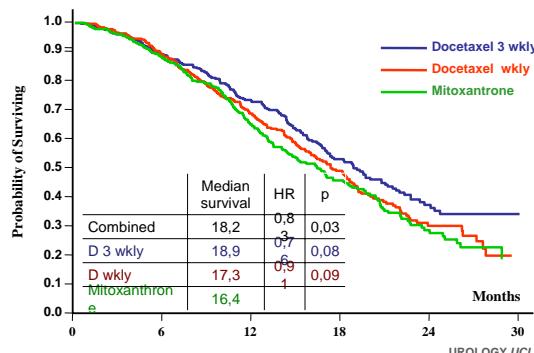
## Docetaxel in prostate cancer

### TAX 327: study design



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## TAX 327: results



## TAX327 ( update 2006)

### Overall results

	Docetaxel Q3W (n=335)	Docetaxel weekly (n=334)	Mitoxantrone (n=337)
Updated data 2006			
% dead	81.5%	80.5%	86.4%
Median Survival (months)	19.3	17.8	16.3
HR	0.79 (0.005)	0.87 (0.10)	

Berthold et al. ASCO Prostate 2007.

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## Docetaxel : conclusions of phase III trials

- ✗ Docetaxel q3w ± EMP demonstrated over mitoxantrone/prednisone:
  - 20–24% reduction in the risk of death
  - Increased PSA response rate
  - Increased QoL improvements
- ✗ Overall, therapy was well tolerated with a predictable adverse-event profile

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## TAX327 ( update 2006)

### Proportion of patients remaining alive at 3 years.

	Docetaxel Q3W (n=335)	Docetaxel weekly (n=334)	Mitoxantrone (n=337)
Data 2006			
3 years survival rate	17.9%	16.7%	13.7%

Berthold et al. ASCO Prostate 2007.

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**JOURNAL OF CLINICAL ONCOLOGY**

**What is more exciting? The activity of docetaxel in early prostate cancer or the successful collaboration between urologists and medical Oncologists to complete a study in early prostate cancer?**

Michael A Carducci  
Division of Medical Oncology, Johns Hopkins,  
Baltimore, MD  
February 28, 2005

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**Is there a life after docetaxel ?**

5 years after the publication of TAX-327

- ✗ The overall benefit is very limited
- ✗ We still don't know when to start chemotherapy
- ✗ We still looking at the best drug to associate with docetaxel
- ✗ We still don't have an effective second line.

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**When to start docetaxel ?**

**TAX 327: survival in subgroups**

Hazard ratio in favor of:  
Docetaxel 3qw | Mitoxantrone

ITT  
Age < 65  
Age ≥ 65  
Age ≥ 75  
Pain no  
Pain yes  
KPS ≥ 80  
KPS ≤ 70

0.2 0.4 0.6 0.8 1 1.2 1.4

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**When to start docetaxel ?**

**Rising PSA as only sign of PD at study entry**

	Docetaxel q 3 w N = 48	Mitox. N = 50
Median Survival (mos) 95% CI	24.1 20.0 - NR	20.8 16.7 - 25.1
Hazard Ratio 95% CI	0.67 0.36 - 1.25	
Hazard Ratio for overall population	0.76	

De Wit, Eur J Cancer 2005

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**When to start docetaxel ?**

Disease Burden

Median Survival

Chemotherapy

No  
Individualize  
Experimental therapy

Yes  
Yes

Beer T, modified

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**Is docetaxel the new gold standard ?**

Drug	phase	Results
Oral Platinum (Satraplatin)	Phase II Phase III	± Stopped
Vinorelbine	Phase III	Equivalent to Mito Better tolerated
Gemcitabine	Phase II combination	Under investigation
Epothilones Ixabepilone (BMS-247550),	Phase II/III	Microtubules stabilizer Promising in taxane resistant patients
Irofulvene	Phase II/III	Ocular Toxicity

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## Estramustine phosphate does not increase the efficacy of docetaxel.



Prospective randomized study comparing docetaxel, estramustine, and prednisone, with docetaxel and prednisone in patients with metastatic hormone-refractory prostate cancer  
 JP Machiels, F.Mazzeo, M.Clausse, B.Filleul, L.Marcelis, B.Honhon, L.D'hont, C.Dopchie, V.Verschaeve, L.Duck, D.Verhoeven, P.Jousten, MA Bonny, AM Moxhon, B. Tombal and J.Kerger  
*J.Clin.Oncol. In Press*

- ✓ RCT in 150 metastatic HRPC in 19 Belgian centers
- ✓ Docetaxel 35 mg/m<sup>2</sup>; d2-d9 triweekly, prednisone 10 mg p.o. oad, estramustine 280 mg p.o. tid J1-5 & J8-J12, dicoumarine 1 mg p.o. daily
- ✓ Docetaxel 35 mg/m<sup>2</sup>; d2-d9 triweekly, prednisone 10 mg p.o.

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## Combinations with docetaxel

Drug	phase	Modality
Thalidomide	II comparative	Antiangiogenesis
Exisulind	I/II	NSAID derivative (inhibition GMPC)
Oblimersen	II/III	antiBCL2
Clusterin	Precclinical	anticlusterin
Calcitriol	II/III	
Atrasentan	I/II	Endothelin inhibitor

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## What to do when docetaxel fails...

- Very rich 2<sup>nd</sup> line portfolio
- Chemotherapy
  - ❖ Mitoxantrone
  - ❖ Navelbine
  - ❖ VP16 ( in neuroendocrine tumours)
  - ❖ Carboplatin (but what is the rational)
  - ❖ Satraplatin
- Targeted therapies

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## Non cytotoxic approaches of Castration Resistant PCa

- ✓ Optimizing intracellular control of androgens
- ✓ Targeting the vasculature
- ✓ Turning the antitumor activity
- ✓ Targeting the bone metastases

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## Continuous ADT fails to maintain low intracellular level of testosterone.

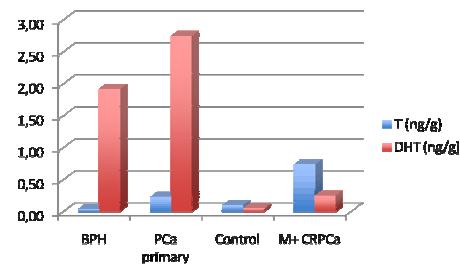


Maintenance of Intratumoral Androgens in Metastatic Prostate Cancer: A Mechanism for Castration-Resistant Tumor Growth  
 RB Montgomery, EA. Mostaghel, R.Vessella, DL. Hess, TF. Kalhorn, CS. Higano, LD. True, PS. Nelson  
*Cancer Res 68(11):4447-54, 2008*

- ✓ Androgen levels and transcripts encoding steroidogenic enzymes in
  - BPH
  - untreated primary PCa,
  - metastases from patients with castration-resistant PCa
  - xenografts derived from castration-resistant metastases.

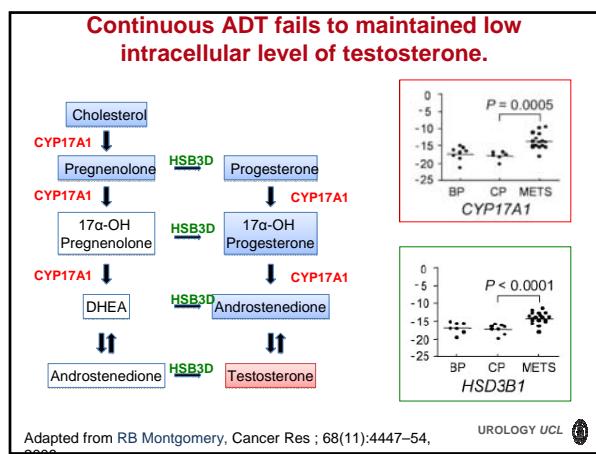
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## Continuous ADT fails to maintain low intracellular level of testosterone.



Adapted from RB Montgomery, *Cancer Res* ; 68(11):4447-54, 2008

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**Continuous ADT fails to maintained low intracellular level of testosterone.**

(...) We conclude that intracrine steroidogenesis may permit tumors to circumvent low levels of circulating androgens. **Maximal therapeutic efficacy** in the treatment of castration-resistant prostate cancer will require novel agents capable of inhibiting intracrine steroidogenic pathways within the prostate tumor Microenvironment (...).

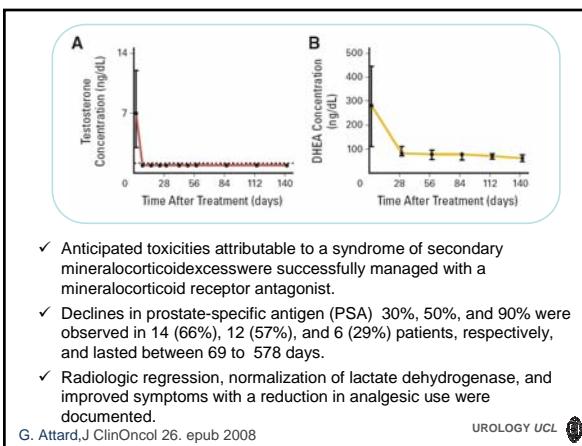
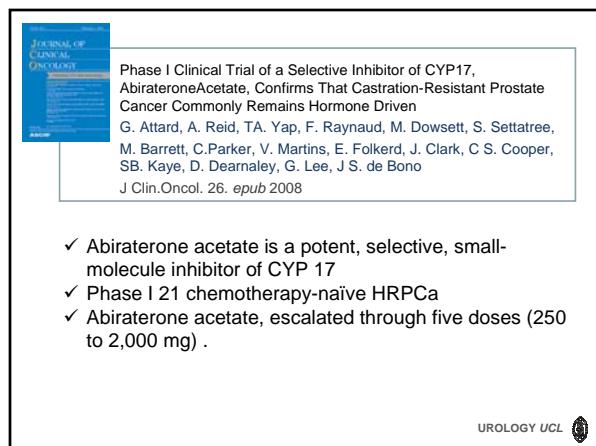
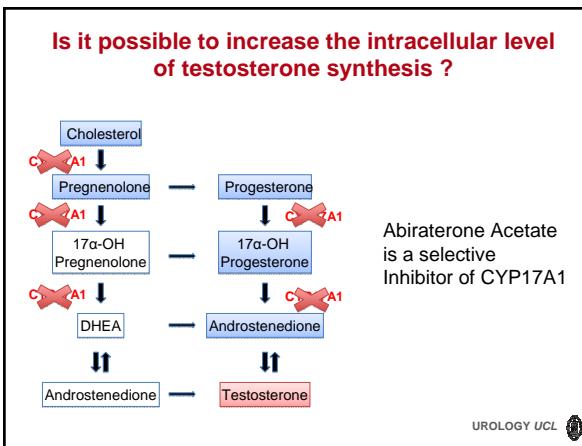
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**Second-line hormonal manipulations**

Second line antiandrogens

Total	Drug	Patients (n)	% > 50% PSA response	Duration (months)
Scher et al	High-dose bicalutamide (150 mg/day)	51	14	4
Joyce et al	High-dose bicalutamide (150 mg/day)	31	23	NA
Kucuk et al	High-dose bicalutamide (150 mg/day)	52	20	NA
Kassouf et al	Nilutamide (200 or 300 mg/d)	28	29	7
Desai et al	Nilutamide (150 or 300 mg/d)	14	50	11
Debruyne et al	Cyproterone acetate (100 mg bid)	161	4	3.6

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## CYP17A inhibition is a old concept !!!

Total	Drug	Patients (n)	% > 50% PSA response	Duration (months)
Small et al	Ketoconazole (400 mg tid) + hydrocortisone	50	63	3.5
Small et al	Ketoconazole (400 mg tid) + hydrocortisone + AAW	20	55	8.5
Small et al	Ketoconazole (400 mg tid) + hydrocortisone + AAW	128	27	8.6
Harris et al	Ketoconazole (200 mg tid) + hydrocortisone	28	46	7.5
Millikan et al	Ketoconazole (400 mg tid) + hydrocortisone + AAW	45	31	NA
Denis et al.	Liarozole (150-300 tid)	85	29	6

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## Non cytotoxic approach of Castration Resistant PCA

- ✓ Optimizing intracellular control of androgens
- ✓ Targeting the vasculature
- ✓ Turning the antitumor activity
- ✓ Targeting the bone metastases

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## Angiogenesis in Prostate Cancer

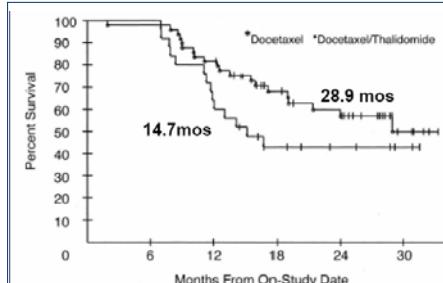
### Thalidomide

regimen	Docetaxel 30 mg/m <sup>2</sup> - 3/4 wks	Docetaxel 30 mg/m <sup>2</sup> - 3/4 wks Thalidomide 200 mg/os d.	p
n	25	50	
% alive at 18 mths	42.9%	62.8%	0.01
TTT (mths)	3.7	5.9	< 0.001
PSA response > 50%	37%	53%	< 0.001
Objective response	17%	11%	

Dahut, JCO 2004

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## Angiogenesis in Prostate Cancer



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Dahut, JCO 2004

## Angiogenesis in Prostate Cancer

Drug	Recept.	Phase	Results
bevacizumab, (Avastin)	VGEF	II/III + docetaxel	awaiting
Thalidomide (Thalomid)		II + docetaxel	20% PSA response
Sunitinib		II + docetaxel	
VEGF-Trap		III + docetaxel	
Sorafenib		II + docetaxel	
IMID, CC-4047,			

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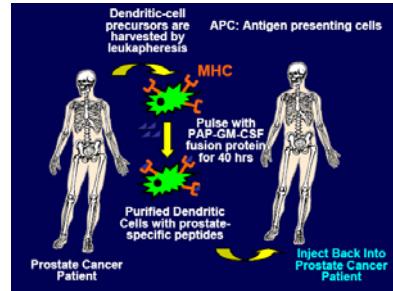
## Vaccine therapy

DESCRIPTION		CLINICAL TESTING PHASE: PATIENT POPULATION
Provenge (APC8015)	Autologous CD54+ dendritic cells loaded with recombinant GM-CSF + PAP fusion protein	Phase 3; randomized, placebo-controlled trial in asymptomatic men with APC showed vaccine to be associated with clinical benefit; phase 3 trial accruing APC patients with Gleason ≤7; ongoing phase 2 trial with bevacizumab in hormone-sensitive prostate cancer
GVAX	Allergenic prostate cancer cell lines (PC-3 and LNCaP) genetically modified to secrete GM-CSF	Phase 2/3; immunogenicity and safety demonstrated in APC patients; currently enrolling symptomatic and asymptomatic APC patients for phase 3 trial
BLP25 liposome vaccine	Synthetic MUC1 peptide + adjuvant (lipid A) incorporated into liposomes	Phase 2; single-institution, single-arm, open-label trial in men with rising PSA after radical prostatectomy
Prostvac-VF	Vaccines and toxoid viral vectors, each containing genes encoding human PSA and 3 costimulatory molecules: LFA-3, ICAM-1, B7.1	Phase 2; randomized, double-blind, placebo-controlled trial in APC patients; vaccine is given in combination with GM-CSF; primary end point is progression-free survival

GM-CSF = granulocyte-macrophage colony stimulating factor; PAP = prostatic acid phosphatase; APC = androgen-independent prostate cancer; PSA = prostate-specific antigen

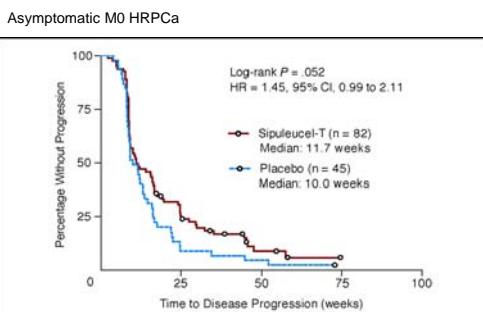
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## APC 8015 - Provenge



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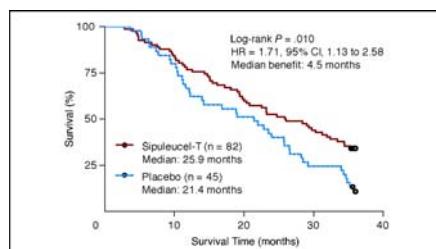
## APC 8015 - Provenge



Small, E. J. et al. J Clin Oncol; 24:3089-3094 2006

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## APC 8015 - Provenge



Less than 10% Grade II – IV toxicities

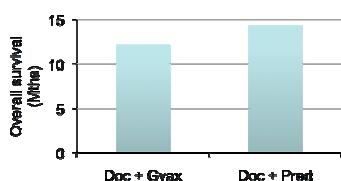
Small, E. J. et al. J Clin Oncol; 24:3089-3094 2006

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## GVAX

A phase III trial of GVAX immunotherapy for prostate cancer in combination with docetaxel versus docetaxel plus prednisone in symptomatic, castration-resistant prostate cancer (CRPC).

The study was prematurely terminated after accrual of 408 pts due to an imbalance in deaths.



Small, E. J. et al. 2009 Genitourinary Cancers Symposium

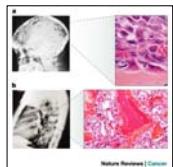
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## Non cytotoxic approach of Castration Resistant PCA

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- ✓ Turning the antitumor activity
- ✓ Targeting the bone metastases

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## Bone metastasis in PCa

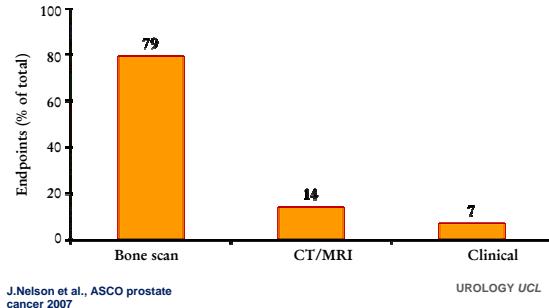


- Present at diagnostic in 5-25% of the patients in country where PSA is used routinely
- 1<sup>st</sup> metastatic site in > 80% of patients
- 1<sup>st</sup> cause of morbidity and mortality
- > 90% osteoblastic
- Most are axial

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## Bone metastasis in PCa

- Confirmed endpoints of progression in non metastatic hormone resistant PCa patients



## Bone Metastases in PCa

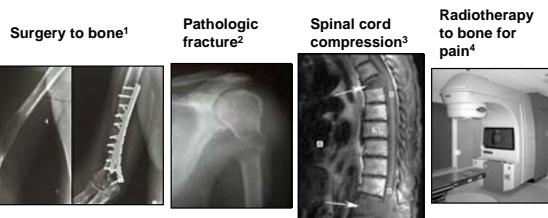
	TAX 327	SWOG9916	Oudard
Bone Mets	91 %	86%	88-98%
Visceral	23%	18%	7-19%
Measurable	40%		
% enroll for progressing on bone	70%		

Petrylak et al., NEJM, 351 (15), 1513, 2004  
Tannock I et al., NEJM 351 (15), 1502, 2004  
Oudard S. et al., JCO 23(15), 2005

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## Metastases to Bone Contribute to Significant Skeletal Morbidity by Causing Skeletal Related Events (SREs)



1. Available at: [http://www.hopkins-arthritis.org/reviews/bone/metastatic\\_bone\\_disease\\_rehounds2.html](http://www.hopkins-arthritis.org/reviews/bone/metastatic_bone_disease_rehounds2.html). Accessed 8/2007 Provided by John Hopkins Arthritis Center at John Hopkins University

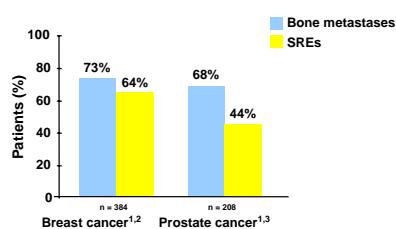
2. Wheeless' Textbook of Orthopedics. [www.wheelessonline.com](http://www.wheelessonline.com) © 2007 Datta Trace Publishing Company. All rights reserved

3. Higdon ML, et al. Am Fam Physician 2006;74:1873-80 Permission obtained

4. This image is licensed under the GNU Free Documentation License

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## High Prevalence of Bone Metastases and SREs in Prostate Cancer



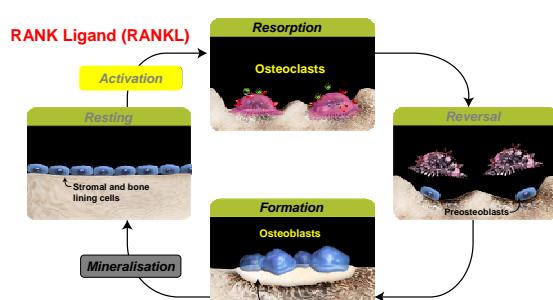
SREs: skeletal related events

47

1. Coleman R. Clin Cancer Res 2006;12:6243-9 2. Lipton A, et al. Cancer 2000;88:1082-90 3. Saad F, et al. J Natl Cancer Inst 2002;94:1459-65

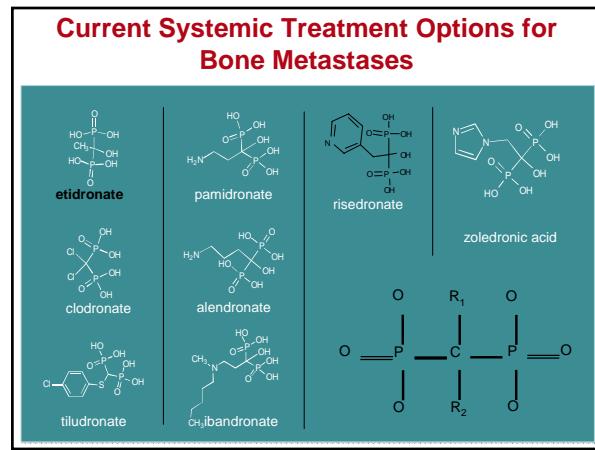
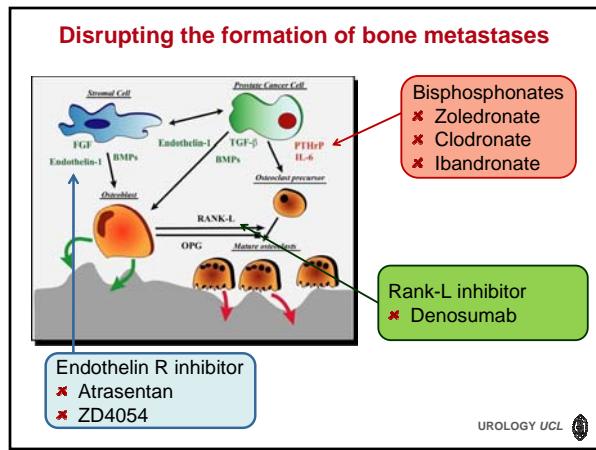
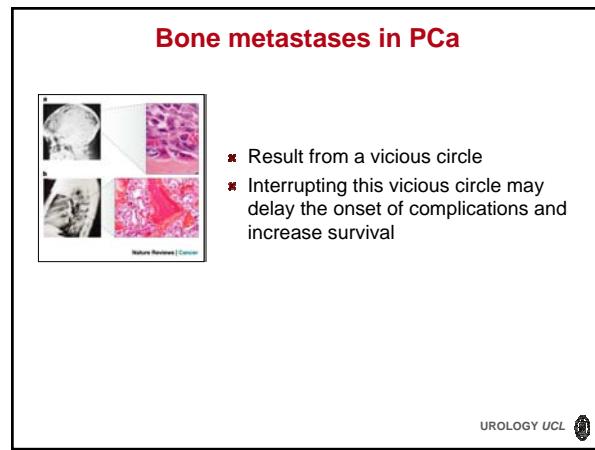
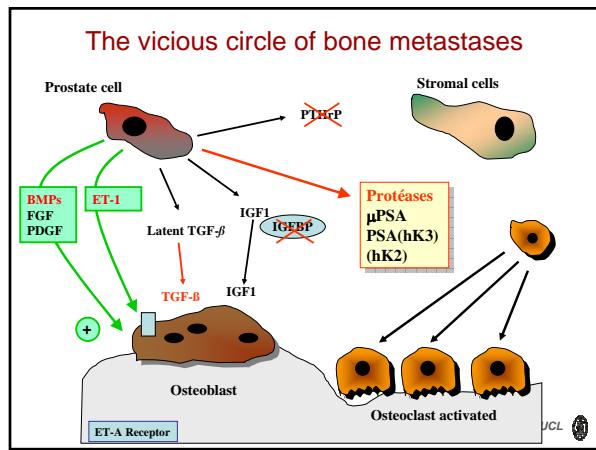
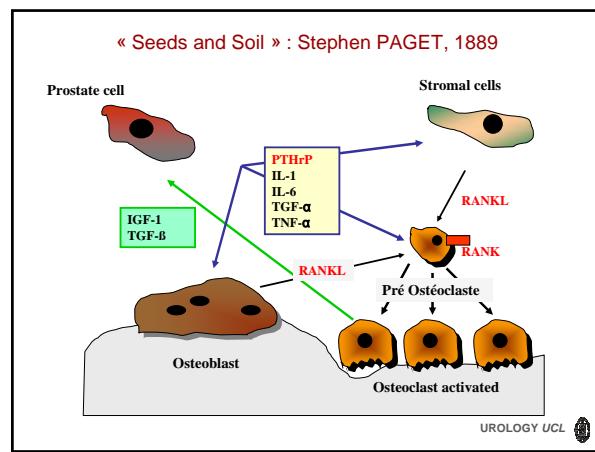
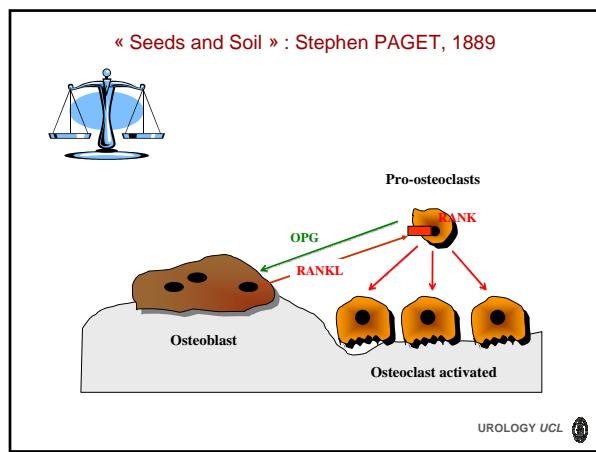
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## Physiologic Balance Between Bone Resorption by Osteoclasts and Bone Formation by Osteoblasts



Adapted from Baron R. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 5th ed. 2003:1-8  
48 - Lg. J Clin Invest 2005;115:3319-3325

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## Bisphosphonates in the Treatment of Bone Metastases From Prostate Cancer

Test drug	N	Results	Reference
Etidronate	57	Transient pain reduction	Smith, 1989, J.Urol
Clodronate	75	Only transient sympt. benefit	Elomaa, 1992, Int. Urol. Nephrol.
Placebo-controlled studies			
Clodronate	311	No significant benefit	Dearnaley, 2003, JNCI
Pamidronate	378	No significant benefit	Small, 2003, JCO
Clodronate	209	No significant benefit	Ernst, 2003, JCO
Zoledronate	643	Significant delay of SRE	Saad, 2002/2004, JNCI

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## Bisphosphonates

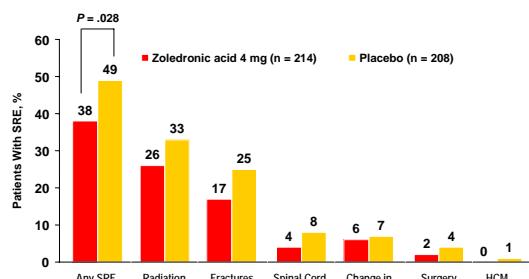
JNCI CANCER SPECTRUM

A Randomized, Placebo-Controlled Trial of Zoledronic Acid in Patients With Hormone-Refractory Metastatic Prostate Carcinoma  
Saad F. et al, JNCI 94, 1458-1468, 2002  
Saad F. et al. JNCI 96, 879-882, 2004.

A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PRO5 Trial).  
Dearnaley et al, JNCI 95:1300-11, 2003.

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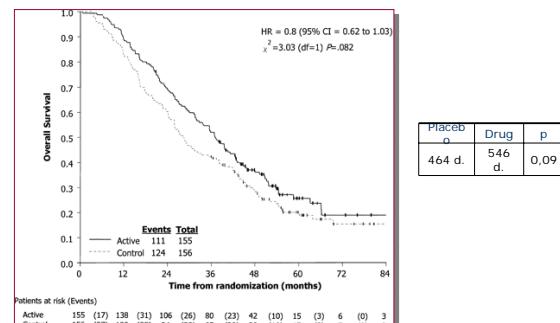
## Zoledronic Acid Reduced All Types of SREs at 2 Years in Patients With Bone Metastases From PC



SRE, skeletal-related event; PC, prostate cancer; HCM, hypercalcemia of malignancy.

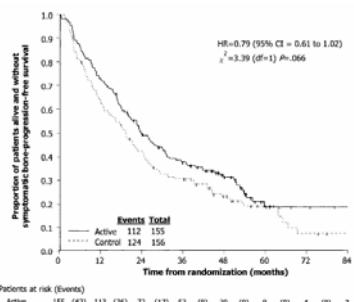
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## Do bisphosphonates increase survival ?



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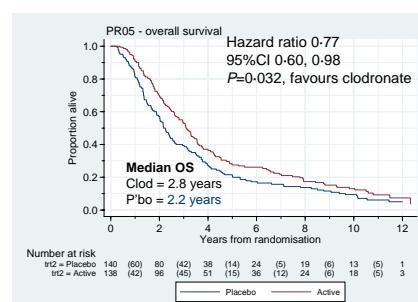
## Clodronate and SRE



Dearnaley et al, JNCI 95:1300-11, 2003.

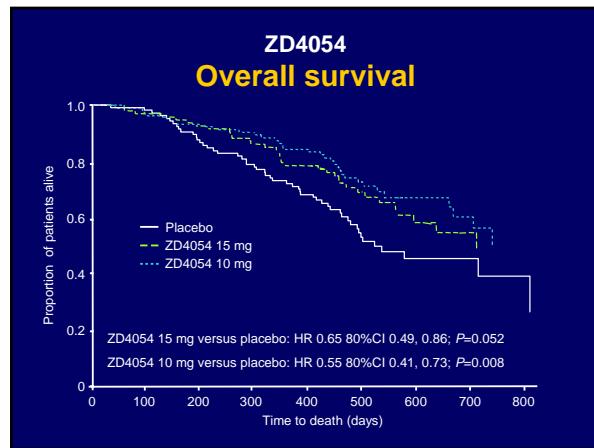
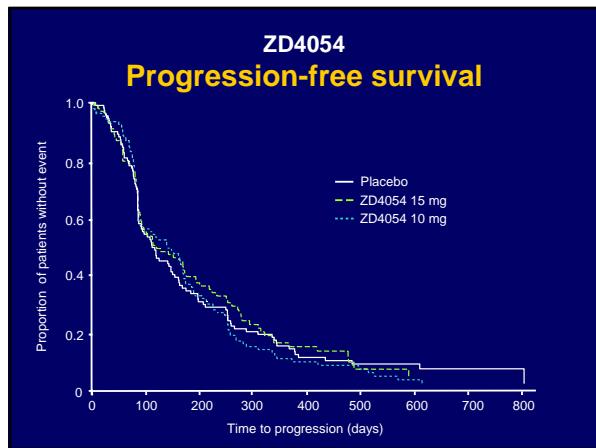
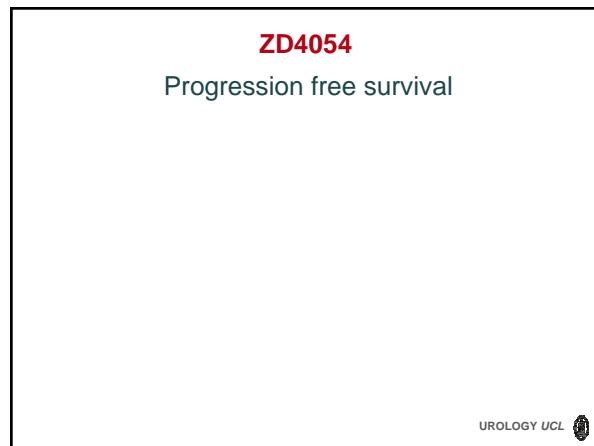
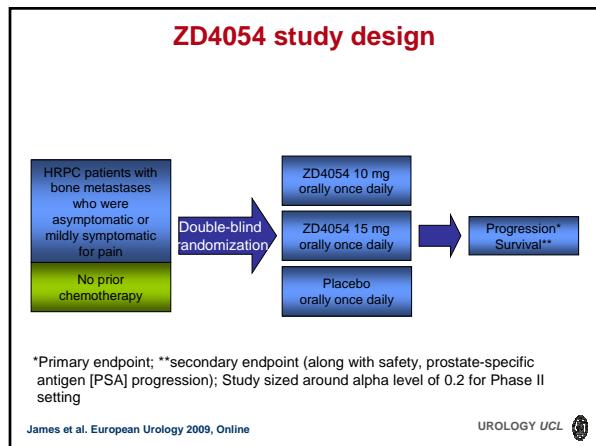
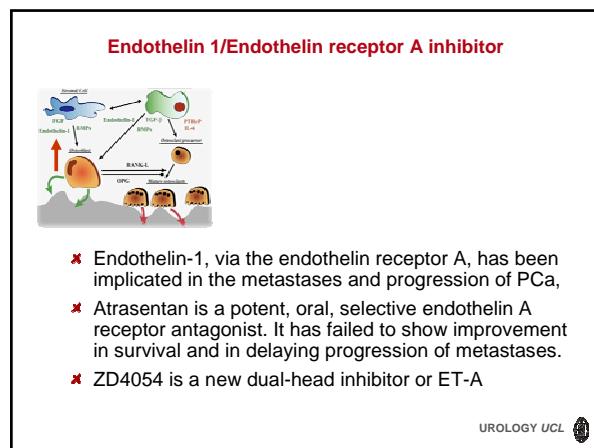
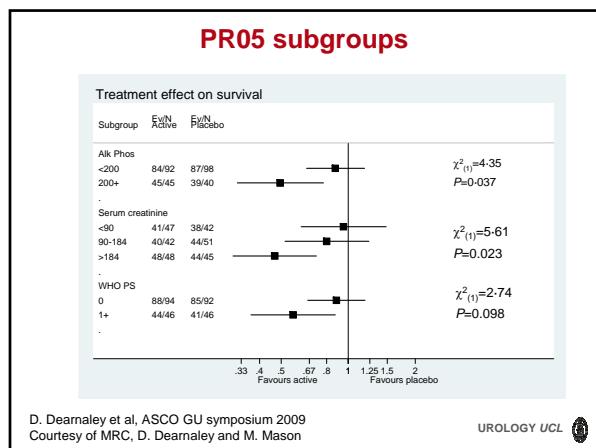
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## PR05 results: overall survival

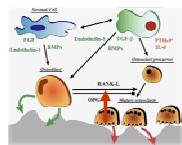


D. Dearnaley et al, ASCO GU symposium 2009  
Courtesy of MRC, D. Dearnaley and M. Mason

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## Rank-L inhibition

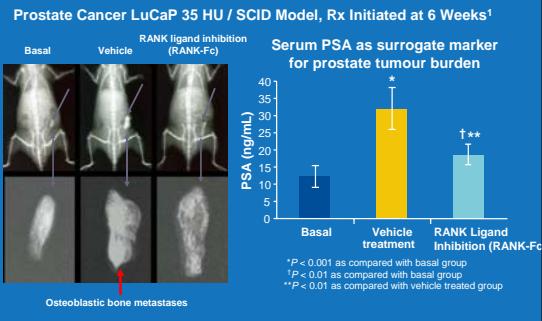


- ✖ Denosumab is a human monoclonal antibody against (RANKL),
- ✖ Denosumab is being studied across a range of conditions, including osteoporosis, treatment-induced bone loss, rheumatoid arthritis, bone metastases, and multiple myeloma.
- ✖ Phase 2 clinical study reporting the clinical effects of denosumab on bone mineral density endpoints in postmenopausal, osteoporotic women.

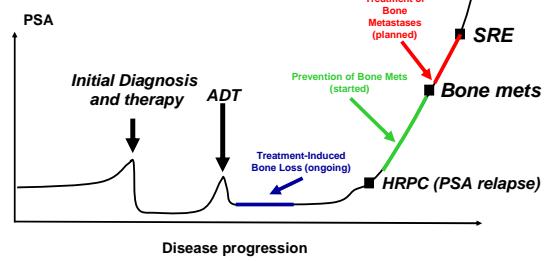
McClung, N Engl J Med. 354(8):821-31, 2006 .

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RANK ligand inhibition Significantly Reduced Serum PSA in a model of prostate cancer-induced bone metastases in mice



## Denosumab trials in PCa



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## How are we going to win over PCa ?

- ✖ Open our mind to new therapeutic modalities
- ✖ Give maximal priority to clinical trials when definitive answer is needed
- ✖ Develop team approach and team spirit



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