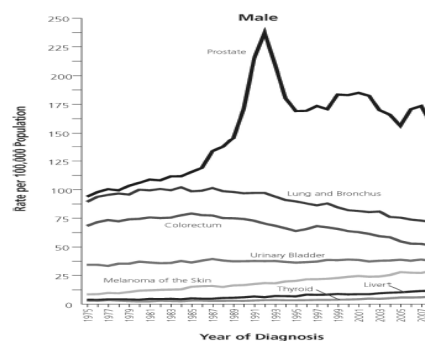


## New Developments in Prostate Cancer: Localized Prostate Cancer

David Sharp, MD  
Assistant Professor  
Urologic Oncology  
Department of Urology  
The Ohio State University's Wexner Medical Center

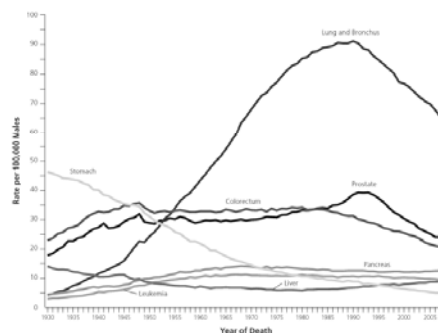
## Age adjusted incidence



## Incidence/ Mortality

- 241,740 men will be diagnosed with prostate cancer in 2012
  - 28,170 men will die
- Lifetime risk: 1 in 6 men diagnosed with prostate cancer during their lifetime (8.6% of men will develop PCa between ages 50 and 70)
- Rates of incidence increased in late 80's, early 90's and have since leveled off
- Mortality has been decreasing in the US since that time

## Age adjusted mortality



## Advances in Localized Prostate Cancer

- Outline various treatment options
- Trends in treatment
- Risk stratification
- Active surveillance
- Focal Therapy
- Imaging advances

## Options for Treatment

- Active surveillance
- Definitive treatment
  - Prostatectomy
    - Open, robotic
  - Radiation
    - External Beam/ IMRT
    - Brachytherapy
    - Proton Beam/ Cyberknife
  - Thermal
    - Cryotherapy
    - High intensity-frequency ultrasound
- Focal therapy
  - Cryotherapy, HIFU, Brachytherapy

Optimal treatment strategy:

- Long term disease control
- Minimal treatment-related morbidity
- Maximum preservation of quality of life

## Options for Treatment

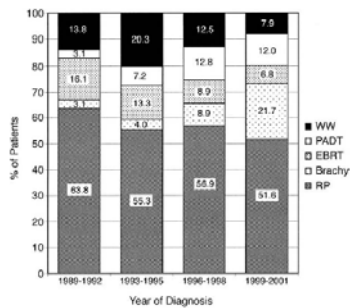
- Active surveillance
- Definitive treatment
  - Prostatectomy
    - Open, robotic
  - Radiation
    - External Beam/ IMRT
    - Brachytherapy
    - Proton Beam/ Cyberknife
  - Thermal
    - Cryotherapy
    - High intensity-frequency ultrasound
- Focal therapy
  - Cryotherapy, HIFU, Brachytherapy

## Selecting Treatment

- Balance risk:
  - Posed by the health and age of the patient
    - Competing causes for death
    - Life expectancy
  - Posed by the cancer and its treatment
    - Any treatment for prostate cancer associated with potential decrement in quality of life

## Trends in Prostate Cancer Therapy

### Low risk Prostate Cancer



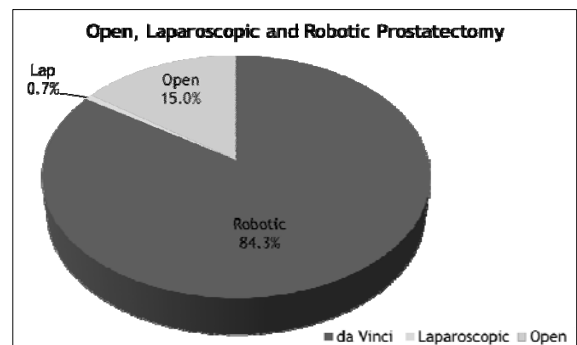
Zerbib, Zelefsky et al, Urology 72, Dec 2008.

Advantages of RP	Disadvantages of RP
Long-term potential for cure	Surgery
Full pathological information	Hospitalization (1 night)
Relief of urinary obstruction	Catheter
'Easy' to follow patients for recurrence	Recovery time
'Peace of mind' knowing the prostate is out	Incontinence
Incontinence and erectile dysfunction treatable	Erectile dysfunction

## Prostatectomy

- Only treatment for localized prostate cancer with Level 1 evidence confirming it improves: Overall survival, CSS, risk of mets, local progression  
Bill-Axelsson, Holmberg, Ruutu et al, NEJM 2005; 352: 1977-1984.
- Surgical advances and anatomic understanding have allowed for decreased morbidity

## Prostatectomy in the U.S.



## Stratification of risk

- Pathologic stage and prognosis prediction
  - Size, extent of the cancer (stage, biopsy results)
  - Grade of tumor (Gleason grade)
  - PSA
- Probability of PSA recurrence after treatment most reliably predicted
  - Might not predict for subsequent clinical events
- Local or distant recurrence
- Cancer-specific and overall survival
- Nomograms and algorithms combine these factors and more

## Active surveillance

- For very low risk (subclinical) prostate cancers, the best therapy may be monitoring the disease
- Patients and physicians may overestimate seriousness of low-risk cancers and lack confidence in accuracy of staging
- Short-term evidence supports the safety and efficacy of active surveillance

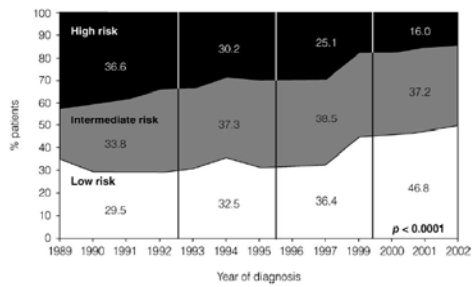
## Stratification of risk

- Molecular markers
  - PSA
  - IL-6 and TGF- $\beta$ 1
  - Urine presence of PCA3
  - TMPRSS2:ERG fusion transcripts

## Watchful waiting vs. Active Surveillance

- Watchful waiting
  - Suggests deferring intervention until symptoms develop
- Active surveillance
  - Suggests close monitoring of
    - PSA
    - PSA change in time
    - changes in digital rectal examination
    - Subsequent biopsies

- Incidence of low-risk disease is increasing

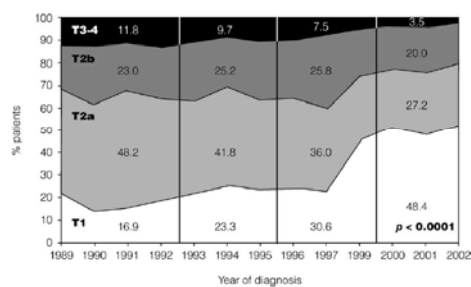


Cooperberg Lubeck et al, J Urol 2003. Data from CaPSURE

## Active surveillance

- Who's a candidate
- Risk of delayed intervention
- Predicting progression
- Psychological impact

- Incidence of lower stage disease is increasing



Cooperberg Lubeck et al, J Urol 2003. Data from CaPSURE

## Active surveillance

- Who's a candidate
- Risk of delayed intervention
- Predicting progression
- Psychological impact

## Who's a candidate

- Identify men who are at 'good risk'
  - Published criteria vary from institution to institution
  - Criteria used at OSU
    - PSA  $\leq$  10 ng/ml
    - Gleason score  $\leq$  6
    - Clinical stage T1 to T2a
    - %positive cores  $<20\%$
    - Extent cancer in any core  $<33\%$
    - PSA prior to biopsy relatively stable (PSAv  $<2$ )

## Active surveillance

- Who's a candidate
- Risk of delayed intervention
- Predicting progression
- Psychological impact

## Who's a candidate

- Rebiopsy often critical
  - Differences between biopsy and pathologic Gleason scores at prostatectomy reduced by extended biopsy
- Consider MRI of prostate to assist with clinical staging

## Risk of delayed intervention

- Prognostic risk assessment not perfect
  - One assumes some risk of disease progression while on active surveillance
- Can treatment be delayed until absolutely necessary without detriment to curability?
  - No differences in adverse pathologic features or PSA recurrence for men with low risk PCa delaying RP up to 180 days
  - No differences in men on active surveillance who eventually underwent RP median 26.5 mo later

Freedland, et al. J Urol. 2006, 175: 1298-1302.  
Warlick, et al. JNCI. 2006, 98: 355-357. .

## Active surveillance

- Who's a candidate
- Risk of delayed intervention
- Predicting progression
- Psychological impact

## Active surveillance

- Who's a candidate
- Risk of delayed intervention
- Predicting progression
- Psychological impact

## Predicting progression

- 'Window of curability'
  - Identify early signs of disease progression so that window remains open
- What constitutes best criteria to monitor not fully determined
- What is the 'trigger' for treatment?
  - PSA velocity
  - PSA doubling time
  - Digital rectal examination
  - Imaging

## Psychological Impact

- *Worry, anxiety, depression*
- PSA 'cripple'
- Untreated cancer in my body
- I'm doing nothing
- Frequent monitoring and rebiopsy worse than treatment

## Psychological Impact

- If I'm going to end up being treated anyway, why wait and worry
- Get it out and get it over with
- Approximately 30% of men received delayed therapy after median of 40 months on active surveillance
- With median follow-up of 42 months, 80% men remained on active surveillance with no prostate cancer-specific deaths or metastatic disease

Roemling, et al. Eur Urol. 2007, 99:1244-1250.  
Hardie, et al. BJU Int. 2005, 95: 956-960.

## Outcomes for surveillance

- Data limited, but reported outcomes to date are promising
- Difficult to study well due to:
  - Slow growth of prostate cancer
  - Time needed to develop metastasis, then death
  - Dissimilar criteria for surveillance
  - Dissimilar parameters monitored
  - Dissimilar triggers to treatment

## Psychological Impact

- Support groups:
  - After adjusting for ethnicity, age, and type treatment, men attending support groups reported better health-related quality of life than men who did not
  - Though intended to provide emotional support, may produce a negative psychosocial response in men when believe pressured by group members to initiate aggressive treatment
- Rethinking prostate cancer
  - Chronic illness rather than instant killer

## Outcomes for surveillance

- Klotz, et al:
  - 300 patients
  - F/U 8 years
  - Overall survival 85%
  - Disease-specific survival 99.3%
- San Francisco
  - 500 patients on surveillance
  - 24% received secondary treatment a median of 3 years (range 1-17 years) after initiating surveillance
  - 38% with increasing Gleason grading on rebiopsy
- Longer-term data with good end-points needed to confirm these results



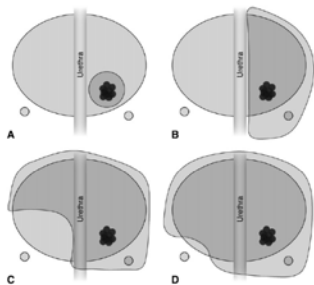
## Role of focal therapy

- Alternative to surgical removal or radiation to the entire gland
  - Only treat the tumor itself “male lumpectomy”
- Focal therapy is attractive
  - Minimize morbidity- sexual and urinary function
- For focal therapy to be viable treatment option
  - Must have accurate staging and grading
  - Precisely locate the cancer within the gland
  - Characterize the risk of the cancer to the individual

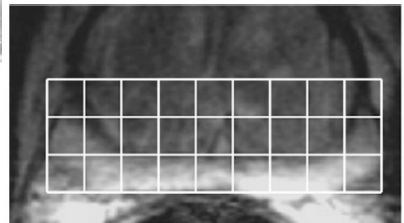
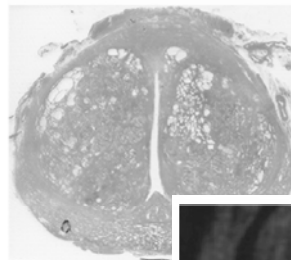
## Barriers to focal therapy

- Precise staging and grading
- Multifocality
- Growth Pattern
- Imaging

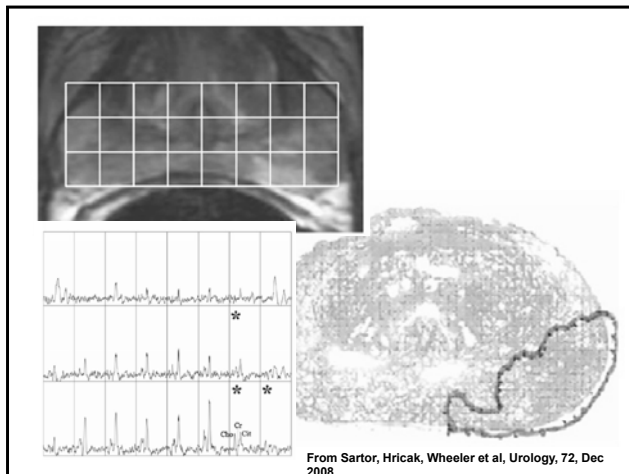
## Focal Therapy



Potential energy sources:  
 Cryoablation  
 High intensity frequency ultrasound (HIFU)  
 Photodynamic therapy  
 Brachytherapy or other radiation source



From Sartor, Hricak,  
 Wheeler et al,  
 Urology, 72, Dec  
 2008



## Transperineal Template Mapping Biopsy (TTMB)

- Performed in OR with template fixed against perineum and with ultrasound guidance- like brachytherapy
  - Set number of cores from standardized locations
  - 20-90 cores
  - Pts at high risk for cancer despite negative transrectal ultrasound-guided biopsy- TTMB >40% positive
- McCracken et al-
  - 100 pts requiring repeat prostate biopsy due to increasing PSA
    - 50 with transrectal saturation biopsy
    - 50 with transperineal template mapping biopsy (TTMB)
    - Cancer detection (46% vs 22%)
    - Complication rate 12 % for TTMB (retention or hematuria) 22% for saturation biopsy (UTI, retention, or hematuria)
- Although more accurate, not commonly performed
  - resource intensive and expensive

- To improve localization of cancer
  - Extended biopsy methods
    - Increase over standard 10-12 core biopsy
    - Many reports of cancer- high grade or with ECE- in RP specimen on side of negative biopsy
    - Image guided (ultrasound or MRI) transrectal “saturation” or transperineal mapping biopsies
    - Necessary over standard TRUS/ BX prior to focal therapy

## Advances in prostate cancer imaging

- Ability to accurately image a cancer in the prostate is significantly limited- difficult to discern cancerous tissue from adjacent normal or BPH tissue.
- It is hoped that with advances in imaging tumors may be better identified within the prostate
  - Identify patients suitable for focal therapy
  - Plan and implement focal treatment
  - Monitor for cancer recurrence and progression

## MRI and MRSI

- Magnetic resonance imaging (MRI) and Magnetic resonance spectroscopy imaging (MRSI) are undergoing continued evaluation
- Prostate cancer has proportionally lower levels of citrate and higher choline and creatinine than areas of BPH or normal prostate—detected by MRSI
- Data suggests improvement in
  - Determining if organ confined (Wang, Hricak, Kattan; Radiology 2006)
  - Assisting with surgical planning (Hricak, Wang, Wei; Cancer 2004)
  - Locating the cancer within the prostate
  - Finding anterior-based cancers missed on biopsy
- Very radiologist and institution dependent and need specialized training in GU MRI interpretation. Inaccuracies still persist.

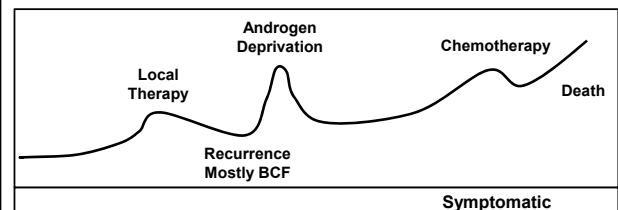
## Advanced Prostate Cancer

**Ahmad Shabsigh, MD**  
 Assistant Professor  
 Department of Urology  
 The Ohio State University's Wexner Medical Center

## Focal Therapy Conclusions

- Attractive potential option
- Although making progress with template biopsies and prostate imaging, more work is necessary before can provide full clinical characterization of prostate cancer that is reliable
- Reasonable to explore in setting of clinical trials

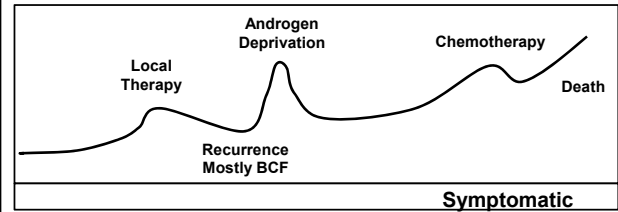
## Natural history of prostate cancer



## Goals of Treatment of Advanced CaP

- Prevent progression (bone mets)
- Prolong survival
- Improve QOL
- Minimize side effects

## Natural history of prostate cancer



## Historically

- Androgen deprivation therapy.
  - LHRH agonists (leuprolide, goserelin, and triptorelin)
  - GnRH receptor antagonist (Degarelix)
  - First generation androgen receptor blockers (Bicalutamide)
- Second line hormonal manipulation: ADT withdrawal, ketoconazole, estrogens

## Historically

- Mitoxantrone + Steroids: 1997
- Docetaxel was the first to show improved survival: 2004
- An artificial pre and post Docetaxel areas of interest

## Bone Protection

- Zoledronic acid
- Denosumab
- Optimal schedule is not defined
  - Poor dentation.
  - SQ vs IV
  - Cost
  - Renal function

## Integrated Data From 2 Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trials of Active Cellular Immunotherapy With Sipuleucel-T in Advanced Prostate Cancer

*Celestia S. Higano, MD; Paul F. Schellhammer, MD; Eric J. Small, MD; Patrick A. Burch, MD; John Nemunaitis, MD; Liannng Yuh, PhD; Nicole Provost, PhD; and Mark W. Frohlich, MD*

## New Therapeutic Agents

- Immunotherapy (Sipuleucel-T)
- Bone targeting agents (Denosumab, Radium-223)
- Androgen pathway (Abiratoerone, MDV3100)

## Sipuleucel-T

- Sipuleucel-T consists of autologous peripheral blood mononuclear cells, including antigen-presenting cells (APCs), which have been activated in vitro with a recombinant fusion protein (prostatic acid phosphatase) linked to granulocyte-macrophage colony-stimulating factor.
- Designed to stimulate an immune response against prostate cancer.

Higano et al. Cancer 2009

## Sipuleucel-T

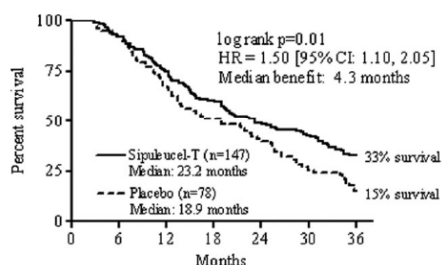


Higano et al. Cancer 2009

## Side Effects

Preferred Term	Any Grade*		Grade 3 or 4*	
	Sipuleucel-T, n=147, No. (%)	Placebo, n=76, No. (%)	Sipuleucel-T, n=147, No. (%)	Placebo, n=76, No. (%)
Any adverse event	145 (98.6)	73 (96.1)	49 (33.3)	21 (27.6)
Chills	86 (57.8)	6 (7.9)	7 (4.8)	0 (0.0)
Fatigue	63 (42.9)	22 (28.9)	2 (1.4)	0 (0.0)
Pyrexia	47 (32.0)	5 (6.6)	3 (2.0)	0 (0.0)
Back pain	33 (22.4)	19 (25.0)	4 (2.7)	1 (1.3)
Headache	28 (19.0)	5 (6.6)	2 (1.4)	0 (0.0)
Arthralgia	22 (15.0)	14 (18.4)	3 (2.0)	0 (0.0)
Asthenia	21 (14.3)	3 (3.9)	0 (0.0)	0 (0.0)
Nausea	21 (14.3)	6 (7.9)	1 (0.7)	0 (0.0)
Anemia	20 (13.6)	8 (10.5)	6 (4.1)	0 (0.0)
Paresthesia	19 (12.9)	7 (9.2)	0 (0.0)	0 (0.0)
Chest wall pain	16 (10.9)	5 (6.6)	3 (2.0)	0 (0.0)
Dyspnea	16 (10.9)	2 (2.6)	5 (3.4)	1 (1.3)
Vomiting	16 (10.9)	2 (2.6)	1 (0.7)	0 (0.0)

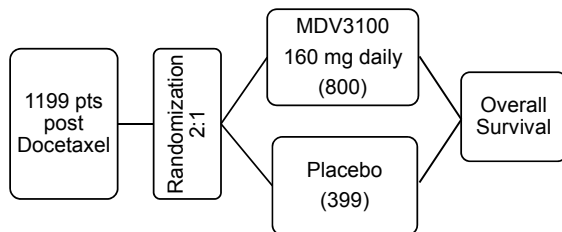
## Sipuleucel-T



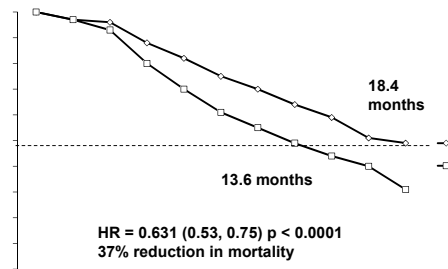
Higano et al. Cancer 2009

## AFFIRM: Phase III of MDV3100 vs Placebo in Post Chemotherapy CRPC

## Study Design



ASCO 2012



ASCO 2012

## AFFIRM Trial

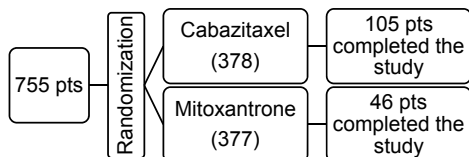
- 156 Centers in 15 countries
- Performance status: 0-2
- 90% power to detect 24% in reduction of mortality
- Interim analysis at 520 events

ASCO 2012

## Prednisone Plus Cabazitaxel Or Mitoxantrone For Metastatic Castration-resistant Prostate Cancer Progressing After Docetaxel Treatment: A Randomised Open-label Trial

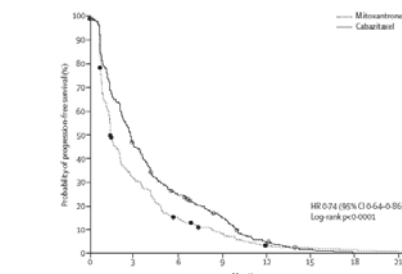
Johann Sebastian de Bono, Stephane Oudard, Mustafa Ozguroglu, Steinbjørn Hansen, Jean-Pascal Machiels, Ivo Kocak, Gwenaëlle Gravis, Istvan Bodrogi, Mary J Mackenzie, Liji Shen, Martin Roessner, Sunil Gupta, A Oliver Sartor

## Study Design



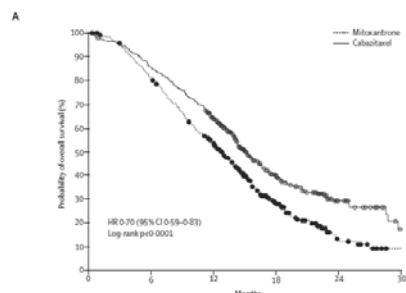
De Bono, Lancet 2011

## Progression Free Survival



De Bono, Lancet 2011

## Overall Survival



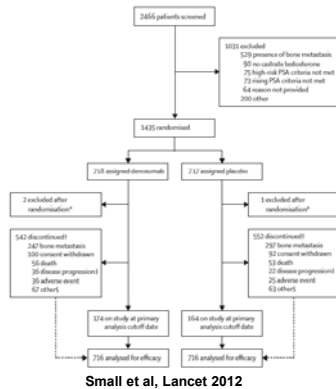
De Bono, Lancet 2011

## Denosumab And Bone-metastasis-free Survival In Men With Castration-resistant Prostate Cancer: Results Of A Phase 3, Randomised, Placebo-controlled Trial

*Matthew R Smith, Fred Saad, Robert Coleman, Neal Shore, Karim Fizazi, Bertrand Tombal, Kurt Miller, Paul Sieber, Lawrence Karsh, Ronaldo Damião, Teuvo L Tammela, Blair Egerdie, Hendrik Van Poppel, Joseph Chin, Juan Morote, Francisco Gómez-Veiga, Tomasz Borkowski, Zhishen Ye, Amy Kupic, Roger Dansey, Carsten Goessl*



## Denosumab



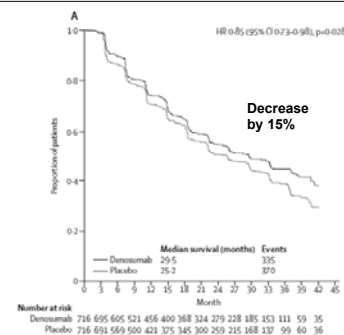
## Exclusion Criteria

- Radiographically detectable bone metastasis.
- Any metastatic involvement of distal organs (LAP is ok).
- IV biphosphonate administration.
- Osteonecrosis/osteomyelitis of the jaw.

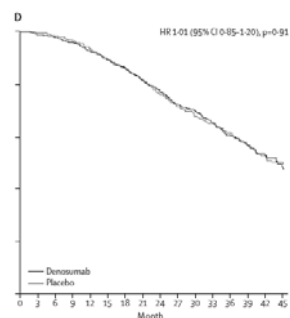
## Inclusion Criteria

- CRPC
- Total serum testosterone level of < 50 ng/dl
- High risk for development of bone metastasis
  - PSA value  $\geq 8$  ng/ml within 3 months before randomization and/or PSA doubling time  $\leq 10$  months

## Development of Bone Mets or death

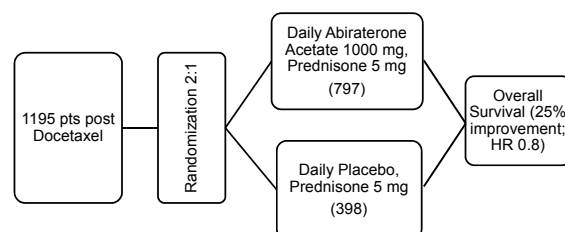


## Overall Survival



Small et al, Lancet 2012

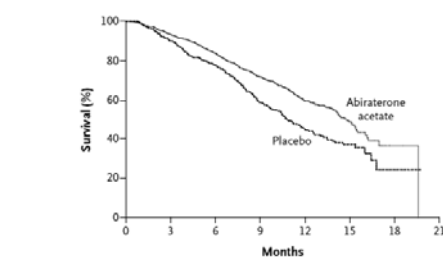
## Study Design



## Abiraterone and Increased Survival in Metastatic Prostate Cancer

Johann S. de Bono, M.B., Ch.B., Ph.D., Christopher J. Logothetis, M.D., Arturo Molina, M.D., Karim Fizazi, M.D., Ph.D., Scott North, M.D., Luis Chu, M.D., Kim N. Chi, M.D., Robert J. Jones, M.D., Oscar B. Goodman, Jr., M.D., Ph.D., Fred Saad, M.D., John N. Staffurth, M.D., Paul Mainwaring, M.D., M.B., B.S., Stephen Harland, M.D., Thomas W. Flaig, M.D., Thomas E. Hutson, D.O., Pharm.D., Tina Cheng, M.D., Helen Patterson, M.D., John D. Hainsworth, M.D., Charles J. Ryan, M.D., Cora N. Sternberg, M.D., Susan L. Ellard, M.D., Aude Fléchon, M.D., Ph.D., Mansoor Saleh, M.D., Mark Scholz, M.D., Eleni Efsthathiou, M.D., Ph.D., Andrea Zivi, M.D., Diletta Bianchini, M.D., Yohann Loriot, M.D., Nicole Chieffo, M.B.A., Thian Kheoh, Ph.D., Christopher M. Haqq, M.D., Ph.D., and Howard I. Scher, M.D.

## Overall Survival

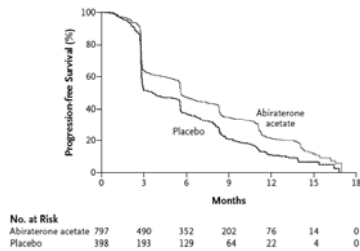


No. at Risk

Abiraterone acetate	797	736	657	520	282	68	2	0
Placebo	398	355	306	210	105	30	3	0

De Bono, NEJM 2011

## Progression Free Survival



De Bono, NEJM 2011

## Radium 223 Chloride (ALSYMPCA trial)

## Side Effects

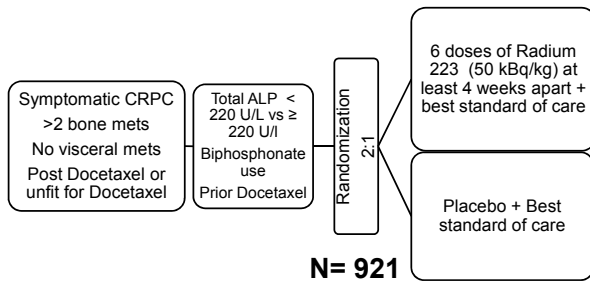
The most common adverse reactions ( $\geq 5\%$ ) reported were

- Joint swelling or discomfort
- Hypokalemia
- Edema
- Muscle discomfort
- Hot flush
- Diarrhea
- Urinary tract infection
- Cough
- Hypertension
- Arrhythmia
- Urinary frequency
- Nocturia
- Dyspepsia
- Upper respiratory tract infection

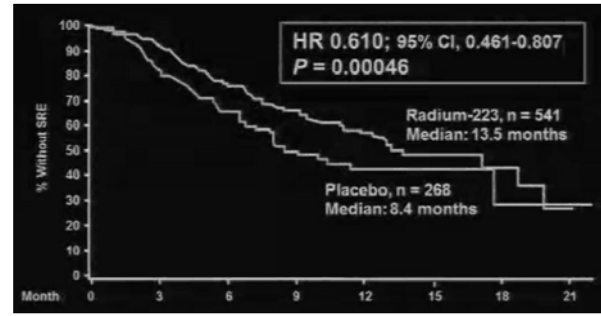
## Radium 223

- Similar to Ca.
- Alpha particles
- 130 center
- 19 countries

## Study Design

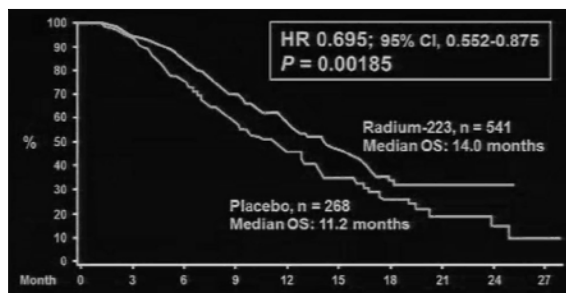


## First Skeletal Related Events



ASCO 2012

## Overall Survival



ASCO 2012

## Advanced Prostate Cancer Conclusions

- Promising new agents with improvement in survival and quality of life
- Sequence of treatments is not clear
- Earlier use maybe better pending clinical trials
- Personalized care.