New targets and drugs in prostate cancer

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San Camillo and Forlanini Hospitals
Rome, Italy
Castration Resistant Prostate Cancer (CRPC)

- Has our perception of CRPC changed with the advent of more effective therapies?

- How has our increasing knowledge about the importance of the androgen receptor (AR) in the progression of prostate cancer helped us?

- Have we commuted a death sentence into a more chronic disease that patients can learn to live with?
Time-line for Prostate Cancer Therapeutics

Huggins Castration

Orchiectomy DES

Shalley* LHRH agonists

Flutamide

Nilutamide

Bicalutamide

Mitoxantrone Docetaxel Zoledronic acid

Sipuleucel-T Cabazitaxel Denosumab (FDA)


* Nobel Prize in 1966
Challenges to developing new drugs for advanced prostate cancer
Bone metastases are difficult to evaluate.
Skeletal-related events (SREs)

- Pathologic Fracture
- Radiotherapy to Bone
- Surgery to Bone
- Spinal Cord Compression
Challenges to developing new drugs for advanced prostate cancer

• Regulatory authorities: survival is the only accepted measure of outcome (no surrogate endpoints)

• Castration Resistant rather than Hormone Refractory

• Inter-patient molecular heterogeneity
  - ETS gene rearrangements (40-70%)
  - PTEN loss cancers (> 50%)
  - RAF rearrangements (~5%)
  - BRCA carrier cancers (<1%)

Most prostate trials have not selected patients on biology
Reason for late Phase III trial failure!

Courtesy of J. de Bono from Attard et al, Cancer Cell. 2009 Dec 8;16(6):458-62
Challenges to developing new drugs for advanced prostate cancer

- PCWG2 (Prostate Cancer Clinical Trials Working Group)
- What surrogate markers should we be measuring in the laboratory?
  - PSA
  - Circulating tumor cells

Fall in CTC count (>5 to <5) associates with improved OS

Cox HR (95% CI) = 2.2 (1.9 - 2.6)  
chi-square = 101.09  
(p-value < 0.0001)

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>N (%)</th>
<th>Months (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;5 CTC at All Draws</td>
<td>88 (38%)</td>
<td>&gt;26 (21.4 to ------)</td>
</tr>
<tr>
<td>2</td>
<td>≥5 CTC at BL &amp; &lt;5 CTC at Last Draw</td>
<td>45 (20%)</td>
<td>21.3 (18.4 to ------)</td>
</tr>
<tr>
<td>3</td>
<td>&lt;5 CTC at Early Draw &amp; ≥5 CTC at Last Draw</td>
<td>26 (11%)</td>
<td>9.3 ( 8.2 to 11.3)</td>
</tr>
<tr>
<td>4</td>
<td>≥5 CTC at All Draws</td>
<td>71 (31%)</td>
<td>6.8 ( 5.8 to 10.3)</td>
</tr>
</tbody>
</table>

*P-values not adjusted for multiple hypothesis tests

Curve Logrank Comparison p-Value*
1 vs. 2 0.1528
1 vs. 3 <0.0001
1 vs. 4 <0.0001
2 vs. 3 <0.0001
2 vs. 4 <0.0001
3 vs. 4 0.5013

Group 1
88 87 84 84 80 76 71 58 47 36 21 7 2 0 0 0 0
Group 2
45 45 44 41 35 32 25 20 13 9 4 3 1 0 0 0
Group 3
26 26 24 20 17 10 7 5 4 3 2 0 0 0 0 0
Group 4
71 65 57 42 31 28 18 12 7 5 2 1 1 0 0 0

# of Patients Still at Risk

21.3m
6.8m

Courtesy of de Bono JS et al, Clin Cancer Res. 2008 Oct 1;14(19):6302-9
Chemotherapy
TAX 327: Updated survival analysis


<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival (months)</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel q3w</td>
<td>19.2</td>
<td>0.79</td>
<td>0.004</td>
</tr>
<tr>
<td>Docetaxel qw</td>
<td>17.8</td>
<td>0.87</td>
<td>0.086</td>
</tr>
<tr>
<td>Mitoxantrone q3w</td>
<td>16.3</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Years**

**Probability of surviving**

**Years**
Metastatic CRPC 1\textsuperscript{st} - line therapy
Current standard of care

- Docetaxel is the standard of care in 1\textsuperscript{st}-line mCRPC\textsuperscript{1,2}
- All patients eventually progress on docetaxel-based chemotherapy
- Approximately 50\% receive 2\textsuperscript{nd}-line chemotherapy\textsuperscript{3,4}
- Until recently, there has been no approved second-line therapy

## Overall Survival with 2\textsuperscript{nd} line chemotherapy for mCRPC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Setting</th>
<th>Patients (N)</th>
<th>Overall survival</th>
</tr>
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<tbody>
<tr>
<td><strong>SPARC</strong></td>
<td>Satraplatin + prednisone vs Placebo + prednisone</td>
<td>Progression after 1 prior chemotherapy regimen</td>
<td>950</td>
</tr>
<tr>
<td><strong>TROPIC</strong></td>
<td>Cabazitaxel + prednisone vs Mitoxantrone + prednisone</td>
<td>Prior Docetaxel</td>
<td>755</td>
</tr>
</tbody>
</table>

SPARC: Progression Free Survival ITT Population (per IRC)

- **Satraplatin + Prednisone**
- **Placebo + Prednisone**

**Median (wks)**
- Satraplatin + Prednisone: 11.1 weeks
- Placebo + Prednisone: 9.7 weeks

**HR:** 0.67 (95% CI: 0.57 - 0.77)

Log-Rank P = 0.0000003

**33% Improvement in PFS**

Sternberg CN, J Clin Oncol. 2009 Nov 10;27(32):5431-8
SPARC Overall Survival

- **Satraplatin + Prednisone**
- **Placebo + Prednisone**

**At Risk**
- **Satraplatin**
  - 635
  - 528
  - 398
  - 288
  - 208
  - 103
  - 50
  - 20
  - 6
  - 3
- **Placebo**
  - 315
  - 262
  - 194
  - 150
  - 105
  - 53
  - 21
  - 10
  - 1
  - 0

**Medians**
- **Satraplatin**
  - 61.3
- **Placebo**
  - 61.4

**Stratified HR: 0.98 (95% CI: 0.84, 1.15)**

**Log-Rank P value = 0.7999**

*Sternberg CN, J Clin Oncol. 2009 Nov 10;27(32):5431-8*
### Overall Survival with 2nd line chemotherapy for mCRPC

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<tr>
<td>TROPIC</td>
<td>Cabazitaxel + prednisone vs Mitoxantrone + prednisone</td>
<td>755</td>
<td>Median OS: 15.1 months vs 12.7 months HR = 0.70 p&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Prior Docetaxel</td>
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TROPIC: Randomized Phase III Trial (n=755)

mCRPC patients progressing during and after treatment with a docetaxel-based regimen

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

Premedication
- cabazitaxel group: antihistamine, steroid, and H₂ antagonist Antiemetic prophylaxis as required

Primary objective: OS; 90% power to detect a HR of 0.75
Secondary objective: PFS

*The protocol was amended after the first 59 patients enrolled to mandate that eligible patients had to have received >225 mg/m² of docetaxel

*Oral prednisone/prednisolone: 10 mg daily

TROPIC – Overall survival (primary end point)

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>MP</th>
<th>CBZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>377</td>
<td>300</td>
<td>188</td>
</tr>
<tr>
<td>378</td>
<td>321</td>
<td>231</td>
</tr>
<tr>
<td>188</td>
<td>90</td>
<td>28</td>
</tr>
<tr>
<td>67</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

- Median OS (months): MP 12.7, CBZP 15.1
- Hazard ratio: 0.70
- 95% CI: 0.59–0.83
- P value: <0.0001

30% reduction in the risk of death

Targeting the Androgen Receptor (AR)
Direct Measurement of Tissue Androgens Confirm The Presence of Sufficient Levels To Activate the Receptor

The Adrenal Androgen Androstenediol Is Present in Prostate Cancer Tissue after Androgen Deprivation Therapy and Activates Mutated Androgen Receptor

Atsushi Mizokami,1 Eietsu Koh,1 Hiroshi Fujita1, Yuji Maeda1, Masayuki Egawa,1 Kiyoshi Koshida,1 Seiichiro Honma,2 Evan T. Keller,3 and Mikio Namiki1

Vol. 10, 440–448, January 15, 2004

Featured Article

The Androgen Axis in Recurrent Prostate Cancer

James L. Mohler,1,2,6,7,8 Christopher W. Gregory,3,5 O. Harris Ford III,3,6 Desok Kim,1 Catharina M. Weaver,3 Peter Petrusz,1 Elizabeth M. Wilson,3,5,6 and Frank S. French1,3,6

Departments of Surgery (Division of Urology), Pathology and Laboratory Medicine, Pediatrics (Laboratories for Reproductive Biology), Cell and Developmental Biology, and Biochemistry and Biophysics, and University of North Carolina-Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina; Department of Urology, State University of New York at Buffalo; and Department of Urologic Oncology, Roswell Park Cancer Center, Buffalo, New York

lower (Wilcoxon, P = 0.0000068, 0.00093, and 0.0089, respectively) in recurrent prostate cancer than in benign prostate, and mean dihydrotestosterone levels, although reduced, remained 1.45 nM. Androgen receptor activation in recurrent prostate cancer was suggested by the androgen-regulated gene product, prostate-specific antigen, at 8.80 ± 10.80 ng/ml tissue. Conclusions. Testosterone and dihydrotestosterone occur in recurrent prostate cancer tissue at levels sufficient to activate androgen receptor. Novel therapies for recurrent prostate cancer should target androgen receptor directly and prevent the formation of androgens within prostate cancer tissue.

Intraprostatic Androgens and Androgen-Regulated Gene Expression Persist after Testosterone Suppression: Therapeutic Implications for Castration-Resistant Prostate Cancer

Elahe A. Mostaghel,1,2 Stephanie T. Page,2,5 Daniel W. Lin,3,5 Ladan Fazli,6 Ilsa M. Coleman,1 Lawrence D. True,1 Beatrice Knudsen,1 David L. Hess,7 Colleen C. Nelson,6 Alvin M. Matsumoto,2,5 William J. Bremner,2 Martin E. Gleave,6 and Peter S. Nelson1
Androgen Receptor and Reactivation

- **AR structure**
- **AR regulation**
- **Targeted AR therapies**
- **AR reactivation**

**Androgen Depletion**
- Androgen Dependent
  - Intratumoral androgen production
- Ligand Hypersensitization
  - 1. AR amplification
  - 2. Cofactor dysregulation
  - 3. GF cross talk
  - 4. AR-Y-P
- Androgen Independent
  - 1. Alternative AR splicing
  - 2. AR mutation

**Co-Act** - inactive

**Antagonists**

- Restored AR signaling

**CRPC**

“Biochemical progression” (rising PSA, AR target gene expression)

AR Splice Variants Offer a Clinically Important Avenue of Castration Resistance

AR splice variants lack the ligand binding domain

Constitutively Active, Androgen Receptor Alternative Splice Variants

- Some AR splice variants are constitutively active; ligand-independent state of activation
  - ARv567es (exon skipped) vs ARfl (full length)

- Not limited to all-or-none expression, broad range of AR full length/AR variant ratios

- AR homodimers and heterodimers can form
  - ARfl-ARfl, ARfl-ARv567es, ARv567es-ARv567es

Watson PA, PNAS, 2010 Sept 28 vol 107, no. 39; 16759-16765
Metastases with AR splice variants are common

- Amplified cDNA from 69 metastases, derived from 13 CRPC patients

- No full-length or variant AR detected in 23 samples (neuroendocrine phenotype, non-AR dependent); of the remaining 46 metastases:
  - 80% expressed ARfl
  - 43% expressed ARv567es
  - 24% expressed ARv7es

- Metastases with AR splice variants are common:
  - 20% expressed only the ARv567es variant
  - 59% AR-positive metastases expressed one or more AR splice variants
  - 92% of patients had a minimum of at least one metastasis that was positive for at least one AR splice variant

# The new antiandrogens

<table>
<thead>
<tr>
<th><strong>Abiraterone Acetate</strong> (phase III studies post and pre docetaxel)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Potent and selective inhibitor of CYP17-α-hydroxylase and C17,20-lyase</td>
<td></td>
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</table>

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<thead>
<tr>
<th><strong>MDV3100</strong> (phase III studies post and pre docetaxel)</th>
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<tbody>
<tr>
<td>- AR antagonist, inhibits nuclear translocation and blocks DNA binding of the receptor and activation</td>
<td></td>
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<tr>
<th><strong>TAK-700</strong> (phase III studies post and pre docetaxel)</th>
<th></th>
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<tbody>
<tr>
<td>- Selective, non-steroidal, small-molecule inhibitor of 17,20-lyase</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th><strong>TOK-001</strong> (phase I/II ARMOR1)</th>
<th></th>
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<tbody>
<tr>
<td>- AR antagonist and AR degrader and a CYP17 lyase inhibitor</td>
<td></td>
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<table>
<thead>
<tr>
<th><strong>SARDS</strong></th>
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<tr>
<td>- selective androgen receptor degraders (destroy the AR receptor)</td>
<td></td>
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<tr>
<th><strong>ARN-509</strong> (phase II/II)</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>- AR antagonist, inhibits nuclear translocation and DNA binding of the receptor</td>
<td></td>
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<table>
<thead>
<tr>
<th><strong>Co-factor antagonists</strong></th>
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</thead>
<tbody>
<tr>
<td>- Target coactivator interaction surfaces - AR antagonists</td>
<td></td>
</tr>
</tbody>
</table>
MDV3100 blocks 3 steps in testosterone signaling:

1. AR binding blocked
2. Nuclear translocation blocked
3. DNA binding and activation blocked

Tumor death

Testosterone synthesis

Testosterone

DNA binding and activation blocked

Cell nucleus

No prednisone required
Waterfall Plot of Best Percent PSA Change from Baseline

Chemotherapy-Naïve (N=65)

62% (40/65) >50% Decline

Post-Chemotherapy (N=75)

51% (38/75) >50% Decline

Scher HI, The Lancet, April 2010; Vol 375, 9724, 1437-1446
AFFIRM Phase III Trial of MDV3100 in Post-Chemotherapy CRPC (n ~1,170)

- mCRPC docetaxel up to 2 lines - 1 with docetaxel
- 2:1

Randomize

- MDV3100 -160 mg QD (n=780)
- Placebo QD (n=390)

1° Endpoint: OS (25% increase 12 to 15 mos)

Biomarkers: CTC enumeration and profiling with outcome

NCT00974311

Scher HI and de Bono JS. Co-PI
PREVAIL Phase III Trial of MDV3100 in asymptomatic or mildly symptomatic mCRPC Pre Chemotherapy (n=1,680)

mCRPC asymptomatic or mildly symptomatic patients < 4 BPI

1:1

MDV3100 160mg QD

Placebo QD

1° end point: OS and PFS
2° end point: time to 1st SRE, time to start cytotoxic chemotherapy

NCT01212991
1st patient enrolled Sept 29, 2010

Beer T and Tombal B, co-PI
Adverse effects of androgen deprivation therapy (ADT)

- Hot flashes
- Loss of libido
- Fatigue
- Anemia
- Obesity
- Sarcopenia
- Diabetes
- Cardiovascular disease
- Osteoporosis/fracture

Keating NL et al, J Clin Oncol. 2006 Sep 20;24(27):4448-56
Long-term side-effects of ADT

Sarcopenic obesity

Bone loss
Abdominal obesity and sarcopenia during ADT

Eugonadal young man
Older man on ADT

What are the long term effects of further androgen suppression?

Targeting Bone
The ‘vicious cycle’ hypothesis of bone destruction in prostate cancer

Prostate tumor cells

Growth factors (eg, PTHrP, IL-6, IL-8)

Bone resorption

Growth factors (PDGF, BMPs, TGF-β, IGFs, FGFs)

Activated osteoclast

RANK Ligand

RANK Ligand

Osteoblast

Ca^{2+}
Denosumab may interrupt the vicious cycle of bone destruction in prostate cancer.
Phase III randomized double-blind study of Denosumab vs Zoledronic acid for bone metastases in CRPC (n=1,904)

**Eligibility:**
- mCRPC
- No prior bisphosphonates

**Stratification:**
- Previous SRE
- PSA < or ≥ 10 ng/mL
- Current chemo

**Randomize 1:1**

**Primary objective:** Efficacy (non-inferiority) (SRE); Secondary objectives: Efficacy (superiority), multiple SRE analysis, safety

Zoledronic acid placebo IV infusion and Denosumab 120 mg SC Q4W

Zoledronic acid 4 mg IV infusion and placebo SC Q4W Q4W

Fizazi K, J Clin Oncol 28:7s 2010 (suppl: abstr LBA 4507)
Denosumab vs Zoledronic acid: Time to SRE (n=1901)

**HR 0.82 (95% CI: 0.71, 0.95)**

\[ P = 0.0002 \text{ (Non-inferiority)} \]

\[ P = 0.008 \text{ (Superiority)} \]

**18% Risk Reduction**

**Proportion of Subjects Without SRE**

**Study Month**

- **Denosumab**: 20.7 months
- **Zoledronic acid**: 17.1 months

**Subjects at risk:**

- **Zoledronic Acid**: 951, 733, 544, 407, 299, 207, 140, 93, 64, 47
- **Denosumab**: 950, 758, 582, 472, 361, 259, 168, 115, 70, 39

Fizazi K, J Clin Oncol 28:18s, 2010 (suppl; abstr LBA 4507) and Lancet. 2011 Feb 24. [Epub ahead of print]
Time to First and Subsequent On-Study SRE

Rate Ratio = 0.82 (95% CI: 0.71, 0.94)

*Events occurring at least 21 days apart

Fizazi K, J Clin Oncol 28:18s, 2010 (suppl; abstr LBA 4507) and Lancet. 2011 Feb 24. [Epub ahead of print]
## Cabozantinib: Bone Scan Evidence of Metastasis With ≥ 1 Post-Baseline Scan

<table>
<thead>
<tr>
<th>Patients With Bone Scan Resolution (Partial or Complete)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td><strong>Maximum tumor change, per mRECIST</strong></td>
</tr>
<tr>
<td><strong>Improvement in bone pain(^b)</strong></td>
</tr>
<tr>
<td><strong>Change in tALP and PSA</strong></td>
</tr>
</tbody>
</table>

NE, not evaluated due to no pain at baseline; PSA, prostate specific antigen; BL, baseline.

\(^a\) Independent radiologist review.

\(^b\) Post-hoc investigator survey of whether pain improved at week 6 and/or week 12.

Smith D, J Clin Oncol 29: 2011 (suppl 7; abstr 127)
Immunotherapy
Sipuleucel-T (Provenge) Therapy with Pulsed Dendritic Cells

Dendritic-cell (APC) precursors are harvested by leukapheresis (day 1)

Pulse with PAP-GM-CSF fusion protein for 40 hrs

Purified Dendritic Cells (APC) with prostate-specific peptides (days 2-3)

Inject Back Into Prostate Cancer Patient (day 3-4)

APC: Antigen presenting cells

COMPLETE COURSE OF THERAPY: Weeks 0, 2, 4

Randomized Phase III IMPACT Trial

Asymptomatic or Minimally Symptomatic Metastatic Castrate Resistant Prostate Cancer (N=512)

Primary endpoint: Overall Survival
Secondary endpoint: Time to Objective Disease Progression

Sipuleucel-T Immunotherapy for CRPC

P = 0.032 (Cox model)
HR = 0.775 [95% CI: 0.614, 0.979]

Median Survival Benefit = 4.1 Mos.

Sipuleucel-T (n = 341)
Median Survival: 25.8 Mos.

Placebo (n = 171)
Median Survival: 21.7 Mos.

Development of PROSTVAC-VF-Tricom

• Vaccinia
  – Potent immunological priming agent

• Fowlpox
  – Minimally/non-cross-reactive with vaccinia
  Enables boosting

• Slightly altered PSA transgene
  – Modified HLA-A2 epitope. Increased HLA-A2 binding and immunogenicity.

• Tricom
  – Lymphocyte function-associated antigen LFA-3 (CD58)
  – Intercellular adhesion molecule ICAM-1 (CD54)
  – Costimulatory molecule for the T-cell receptor B7.1 (CD80)

Randomized Phase II Study (Prostvac)

Asymptomatic or Minimally Symptomatic Metastatic Castrate Resistant Prostate Cancer (N=125)

2:1

PROSTVAC-VF Tricom + GMCSF

Treated at physician discretion

Treated at physician discretion and/or Salvage Protocol

Kantoff PW, J Clin Oncol. 2010 Mar 1;28(7):1099-105
Progression-Free Survival

Hazard Ratio = 0.88 (95% CI 0.57 to 1.38)
P = 0.60 (stratified logrank)

Kantoff PW, J Clin Oncol. 2010 Mar 1;28(7):1099-105
Overall Survival

Hazard Ratio = 0.56 (95% CI 0.37 to 0.85)
P = 0.006 (stratified logrank)

Control
- N: 40
- Deaths: 37
- Median: 16.6 months

PROSTVAC
- N: 82
- Deaths: 65
- Median: 25.1 months

Kantoff PW, J Clin Oncol. 2010 Mar 1;28(7):1099-105
Phase III Prostvac Trial Design

Non/Minimally symptomatic Metastatic Castration Resistant Prostate Cancer

PROSTVAC-(V)(F) TRICOM + low dose adjuvant GM-CSF

PROSTVAC-(V)(F) TRICOM Adjuvant placebo

Vector Placebo Adjuvant placebo

Standard of Care

No cross Over

PIs: James Gulley and Philip Kantoff
New Agents and Trials for CRPC

**Pre-docetaxel**
- Abiraterone
- MDV3100
- Sipuleucel-T
- PROSTVAC
- Zibotentan
- Ipilimumab
- Tasquinimod
- TAK 700

**Docetaxel**
- Dasatinib
- Atrasentan
- Zibotentan
- Afiblercept
- Lenalidomide
- OGX-011

**Post-docetaxel**
- Abiraterone
- Cabazitaxel
- MDV3100
- Ipilimumab
- Tak-700
- Sunitinib

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2Kantoff PW, J Clin Oncol 2010; 28:1099–105  
4Chi KN, J Clin Oncol; 28:4247-4254.  
5de Bono J,. NEJM (in press),  
6de Bono J, Lancet. 2010 Oct 2;376(9747):1147-54,  
7Scher HI, The Lancet, April 2010; Vol 375, 9724, 1437 - 1446
Treatment options for patients with CRPC

1 Saad F, J Natl Cancer Inst 2002;94:1458–68
4 Kantoff PW, 2010 Jul 29;363(5):411-22
5 de Bono JS, NEJM (in press)
6 Fizazi K, Lancet. 2011 Feb 24

Zoledronic Acid ¹
Docetaxel ²

Sipuleucel-T ⁴
Cabazitaxel ³
Denosumab ⁶

Abiraterone⁵
MDV3100

The near future

2002 2004 . . . . . . . . . . . . . . . . . . . . . . 2010 2011

Docetaxel
Zoledronic Acid
Sipuleucel-T
Cabazitaxel
Denosumab
Abiraterone
MDV3100
Conclusions in mCRPC

• We have unequivocal evidence of continued involvement of the AR signaling axis

• We still need to address prostate cancer heterogeneity to move the field forward

• We need further long term follow-up to evaluate cardiovascular and metabolic toxicities

• Prostate cancer is not yet a chronic disease, but we are making progress