Managing Castration-Resistant Prostate Cancer: Understanding the Therapeutic Landscape

Michael E Hurwitz, MD, PhD

Relevant financial relationships in the past twelve months by presenter or spouse/partner:
Advisory Board: Nektar Therapeutics
Other: Pfizer

Talk outline

• Biology of metastatic prostate cancer
• Currently used agents
• Sequencing of agents
• Novel agents and strategies
Talk outline

- Biology of metastatic prostate cancer
- Currently used agents
- Sequencing of agents
- Novel agents and strategies

Natural history of prostate cancer

init. therapy: e.g. surgery or radiation

ADT

CRPC

Time

PSA/tumor burden

Death

AIPC
Castration Resistant Prostate Cancer (CRPC)

- CRPC = rising PSA through:
  - LHRH agonist monotherapy
  - LHRH antagonist therapy
  - CAB (LHRH agonist + anti-androgen)

- Used to be called Androgen Independent Prostate Cancer (AIPC)

- We continue LHRH agonist (or antagonist) therapy through all subsequent therapies

ADT side effects

<table>
<thead>
<tr>
<th>side effect</th>
<th>prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>osteopenia</td>
<td>39 (at 2 years)</td>
</tr>
<tr>
<td>osteoporosis</td>
<td>53 (at 2 years)</td>
</tr>
<tr>
<td>bone fracture</td>
<td>15.1-19.4</td>
</tr>
<tr>
<td>metabolic-like syndrome</td>
<td>55</td>
</tr>
<tr>
<td>central weight gain</td>
<td>75</td>
</tr>
<tr>
<td>muscle loss</td>
<td>20.0-22.8</td>
</tr>
<tr>
<td>cardiovascular disease</td>
<td>poorly defined</td>
</tr>
<tr>
<td>hot flashes</td>
<td>44-80</td>
</tr>
<tr>
<td>gynecomastia</td>
<td>12.7-13.3</td>
</tr>
<tr>
<td>mastodynia</td>
<td>19</td>
</tr>
<tr>
<td>decreased libido</td>
<td>58.0-91.4</td>
</tr>
<tr>
<td>decrease in genital size</td>
<td>93</td>
</tr>
<tr>
<td>fatigue</td>
<td>poorly defined</td>
</tr>
<tr>
<td>cognitive changes</td>
<td>19-48</td>
</tr>
<tr>
<td>depression</td>
<td>13</td>
</tr>
<tr>
<td>anemia</td>
<td>13 (&gt;25% decrease)</td>
</tr>
</tbody>
</table>

Walker et al, Clin Genitourinary Cancer 2013
**Is it truly CRPC?**

LHRH Agonist failure

Check Testosterone Level

If Testosterone >20 ng/ml, consider LHRH antagonist*

*The only antagonist is degarelix

**Talk outline**

- Biology of metastatic prostate cancer
- Currently used agents
- Sequencing of agents
- Novel agents
# Treatment classes for mCRPC

- **Blocking androgen signaling:**
  - abiraterone acetate
  - enzalutamide
- **Immunotherapy:** Sipuleucel-T
- **Bone targeting:** Radium-223
- **Chemotherapy**
  - Docetaxel
  - Cabazitaxel
  - Mitoxantrone
Androgen receptor signaling

AR Target Genes

survival
proliferation
PSA

T = testosterone
DHT = dihydrotestosterone
AR = androgen receptor
ARE = androgen response element

Androgen production

Hypothalamus
LHRH
Pituitary
LH
Testes
Testosterone 50-90%

Adrenals DHEA et al 10-50%
Prostate/Tumor
Tumor
Androgen production

Androgen blockade
Cyp17A inhibition

- Abiraterone acetate
  - Potent inhibitor of extragonadal (and gonadal) production of testosterone (i.e. adrenals and intratumoral)
  - 1000 mg/day taken with 5 mg prednisone bid
  - Has replaced ketoconazole

**Abiraterone action**

\[ \text{DHEA} = \text{dihydroepiandrostenedione} \quad \text{T} = \text{testosterone} \quad \text{DHT} = \text{dihydrotestosterone} \quad \text{AR} = \text{androgen receptor} \]
Cyp17A inhibition: abiraterone acetate

pre-docetaxel OS 34.7 vs. 30.3 mo

post-docetaxel OS 14.8 vs. 10.9 mo

Androgen receptor blockade: enzalutamide

- anti-androgen
- much more potent than older anti-androgens
- blocks most nuclear translocation and DNA-binding
- 160 mg po daily
- Side effects: lowers seizure threshold, fatigue
Enzalutamide: a true competitive inhibitor

DHEA = dihydroepiandrosterone  T = testosterone  DHT = dihydrotestosterone  AR = androgen receptor

Beer et al., NEJM, 2014
Scher et al., NEJM, 2012

Androgen receptor blockade: enzalutamide

pre-docetaxel OS 32.4 vs. 30.2 mo

post-docetaxel OS 18.4 vs. 13.6 mo

Baer et al., NEJM, 2014
Scher et al., NEJM, 2012
AR signaling inhibition responses

![Graph showing PSA decline from baseline over time for different treatment groups.]


Rathkopf and Scher, Cancer J 2010

Treatment classes for mCRPC

- Blocking androgen signaling:
  - abiraterone acetate
  - enzalutamide
- **Immunotherapy: Sipuleucel-T**
- Bone targeting: Radium-223
- Chemotherapy
  - Docetaxel
  - Cabazitaxel
  - *Mitoxantrone*
Sipuleucel-T: cellular immunotherapy

Immune therapy: sipuleucel-T

- For rising PSA and asymptomatic or minimally symptomatic disease
- 2-week cycles x3
- Few side effects
- No effect on PSA or PFS but OS 25.8 vs. 21.7 mo

Kantoff et al., NEJM 2010
Maddan et al. The Oncologist 2010
Treatment classes for mCRPC

• Blocking androgen signaling:
  – abiraterone acetate
  – enzalutamide
• Immunotherapy: Sipuleucel-T
• Bone targeting: Radium-223
• Chemotherapy
  – Docetaxel
  – Cabazitaxel
  – Mitoxantrone

\[ Radium \text{ dichloride} \]

– α-emitting isotope that targets bony lesions
– pts with symptomatic bony mets requiring analgesic medications and no visceral disease
– 56% of pts will have improvement in bone pain after 2 doses
– side effects minimal, but … nausea

OS: 14.9 vs 11.3 mo
1st SRE*: 15.6 vs 9.8 mo

\*SRE = skeletal-related event

Parker et al., NEJM, 2013
Treatment classes for mCRPC

- Blocking androgen signaling:
  - abiraterone acetate
  - enzalutamide
- Immunotherapy: Sipuleucel-T
- Bone targeting: Radium-223
- Chemotherapy
  - Docetaxel
  - Cabazitaxel
  - Mitoxantrone

chemotherapy: docetaxel

- stabilizes microtubules
- 75 mg/m² every 3 weeks with 10 mg prednisone daily
- side effects: fatigue, neuropathy, hair loss, nausea

SWOG 99-16 OS: 17.5 vs 15.6 mo

TAX327 OS: 18.9 vs 16.5 mo

Petrylak et al., NEJM, 2004
Tannock et al., NEJM, 2004
Intermittent vs continuous docetaxel

PRINCE: A phase III study comparing intermittent docetaxel therapy versus continuous docetaxel therapy in patients with castration-resistant prostate cancer


Department of Urology, Charité, University Medicine Berlin
Department of Urology, Hospital Welden
Department of Urology, Hospital Bremen-Mitte
Department of Urology, University Hospital Cologne
Department of Urology, University Hospital Düsseldorf
Institute for Clinical Epidemiology and Applied Biometrics, University Hospital Tübingen

Presented By Hannes Cash at 2016 ASCO Annual Meeting

Intermittent vs continuous docetaxel

PRINCE: Study Design

**Intermittent docetaxel**
- 12 week sequence
- 3-weekly: 4 cycles
- Weekly: 3 cycles

**Treatment Holiday**
- until disease progression

**Intermittent docetaxel**
- 12 week sequence
- 3-weekly: 4 cycles
- Weekly: 3 cycles

**Continuous docetaxel**
- 3-weekly regimen
- Weekly regimen

**Disease Progression**:
- 50% PSA increase (at least > 4ng/ml) compared to baseline
- Radiological progression (RECIST)
- Symptomatic progression

Presented By Hannes Cash at 2016 ASCO Annual Meeting

Presented By Hannes Cash at 2016 ASCO Annual Meeting
Intermittent vs continuous docetaxel

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Intermittent docetaxel</th>
<th>Continuous docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>18.3</td>
<td>19.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>15 to 21.5</td>
<td>16.9 to 21.7</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>1.14</td>
<td>1.14</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.75 to 1.72</td>
<td>0.75 to 1.72</td>
</tr>
<tr>
<td>P-value (HR &gt; 1.25)</td>
<td>P&lt;.05</td>
<td>P&lt;.05</td>
</tr>
</tbody>
</table>

Post-hoc analysis
non-inferiority margin 1.25

Non-inferiority not achieved

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One Year Survival

<table>
<thead>
<tr>
<th></th>
<th>Intermittent docetaxel</th>
<th>Continuous docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>One year survival (%)</td>
<td>78</td>
<td>75</td>
</tr>
<tr>
<td>95% CI</td>
<td>67 to 88</td>
<td>64 to 85</td>
</tr>
</tbody>
</table>

Non-inferiority analysis
Difference one year survival (%) 3 (-12 to 18)
95% CI 
P-value (HR diff < -12.5) .0215

Non-inferiority of intermittent docetaxel

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Intermittent vs continuous docetaxel

**Progression Free Survival**

Intermittent clearly non inferior to continuous docetaxel (nearly superior)

![Progression Free Survival Graph](image)

**Time to Treatment Failure**

Intermittent docetaxel comparable to continuous docetaxel

![Time to Treatment Failure Graph](image)
Chemotherapy: cabazitaxel

- decreased binding to P-glycoprotein (vs docetaxel)
- 25 mg/m² every 3 weeks with prednisone daily
- pegfilgrastim standard after each dose
- Compared to docetaxel: less neuropathy/more grade 3-4 toxicity

OS: 15.1 vs 12.7 mo

Cabazitaxel 20 vs 25 mg/m²

**PROSELICA: Study Design**

- mCRPC patients progressing during and after treatment with a docetaxel-based regimen
- N = 1,200
- 172 centers worldwide

CBZ 20 + PRED
- Cabazitaxel 20 mg/m² Q3W
- prednisone 10 mg/d for 10 courses
- n = 598

CBZ 25 + PRED
- Cabazitaxel 25 mg/m² Q3W
- prednisone 10 mg/d for 10 courses
- n = 602
Cabazitaxel 20 vs 25 mg/m²

PROSELICA: Overall Survival

**Median OS, months (95% CI)**
- CBZ 20 + PRED: 13.2 (12.19–14.81)

**HR (20 vs 25): 1.024**
- One-sided 99.9% upper-bound CI: 1.184 within the non-inferiority margin (1.214)

Cabazitaxel 20 vs 25 mg/m²

PROSELICA: Progression-free Survival

**Median PFS, months (95% CI)**
- CBZ 20 + PRED: 2.9 (2.79–3.45)
- CBZ 25 + PRED: 3.5 (3.12–3.94)

**HR (20 vs 25): 1.099 (0.974–1.24)**
**Cabazitaxel 20 vs 25 mg/m²**

**PROSELICA: PSA Response**

- **CBZ 20**
  - 29.5% (160/543)
- **CBZ 25**
  - 42.9% (231/538)

P < 0.0001

Assessed in evaluable patients with baseline ≥ 10 ng/ml and at least one post-baseline measurement.

**Docetaxel vs Cabazitaxel**

**FIRSTANA: Study Design**

- **mCRPC and no prior chemotherapy**
  - N = 1,168 pts
  - 159 centers worldwide

- **CBZ 20 + PRED**
  - Cabazitaxel 20 mg/m² Q3W + prednisone 10 mg/d
  - n = 389

- **CBZ 25 + PRED**
  - Cabazitaxel 25 mg/m² Q3W + prednisone 10 mg/d
  - n = 388

- **DOC + PRED**
  - Docetaxel 75 mg/m² Q3W + prednisone 10 mg/d
  - n = 391
Docetaxel vs Cabazitaxel

**FIRSTANA: Overall Survival**

- **DOC + PRED**
- **CBZ 20 + PRED**
- **CBZ 25 + PRED**

Median OS, months (95% CI)
- **DOC + PRED**: 24.3 (22.18–27.60)
- **CBZ 20 + PRED**: 24.5 (21.75–27.20)
- **CBZ 25 + PRED**: 25.2 (22.90–26.97)

- **CBZ 20 vs DOC**: HR 1.009 (0.85–1.197)  
  \( P = 0.9967 \)
- **CBZ 25 vs DOC**: HR 0.97 (0.819–1.16)  
  \( P = 0.7574 \)

**FIRSTANA: Progression-free Survival**

- **DOC + PRED**
- **CBZ 20 + PRED**
- **CBZ 25 + PRED**

Median PFS, months (95% CI)
- **DOC + PRED**: 5.3 (4.86–5.78)
- **CBZ 20 + PRED**: 4.4 (3.91–5.09)
- **CBZ 25 + PRED**: 5.1 (4.60–5.72)

- **CBZ 20 vs DOC**: HR 1.063 (0.913–1.236)  
  \( P = 0.4218 \)
- **CBZ 25 vs DOC**: HR 0.989 (0.849–1.152)  
  \( P = 0.8035 \)

PFS defined as tumor progression, PSA progression, pain progression or death from any cause.
Docetaxel vs Cabazitaxel

**FIRSTANA: Tumor Response Rate (RECIST)**

<table>
<thead>
<tr>
<th>Patients</th>
<th>DOC + PRED</th>
<th>CBZ 20 + PRED</th>
<th>CBZ 25 + PRED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30.9%</td>
<td>32.4%</td>
<td>41.6%</td>
</tr>
<tr>
<td></td>
<td>54/175</td>
<td>61/188</td>
<td>72/173</td>
</tr>
</tbody>
</table>

Assessed in patients with measurable disease at baseline and with evaluable data to meet the criteria for RECIST derivation.

Presented by: Oliver Sartor

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**FIRSTANA: TEAEs in ≥ 5% of Patients cont.**

<table>
<thead>
<tr>
<th>TEAEs reported in ≥ 5% of patients, n (%)</th>
<th>DOC + PRED N = 387</th>
<th>CBZ 20 + PRED N = 369</th>
<th>CBZ 25 + PRED N = 391</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3–4</td>
<td>All Grades</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>97 (25.1)</td>
<td>8 (2.1)</td>
<td>43 (11.7)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>24 (6.2)</td>
<td>0</td>
<td>25 (6.8)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>15 (3.9)</td>
<td>0</td>
<td>28 (7.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>31 (8.0)</td>
<td>4 (1.0)</td>
<td>33 (8.9)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>25 (6.5)</td>
<td>6 (1.6)</td>
<td>31 (8.4)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>72 (20.4)</td>
<td>6 (1.6)</td>
<td>36 (9.8)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>19 (4.9)</td>
<td>1 (0.3)</td>
<td>17 (4.6)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>151 (39.0)</td>
<td>0</td>
<td>33 (8.9)</td>
</tr>
<tr>
<td>Nail disorder</td>
<td>35 (9.0)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

Presented by: Oliver Sartor
Talk outline

- Biology of metastatic prostate cancer
- Currently used agents
- **Sequencing of agents**
- Novel agents and strategies

Considerations for sequencing of agents

<table>
<thead>
<tr>
<th>agent</th>
<th>eligibility</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone acetate</td>
<td>requires 10 mg prednisone qd</td>
<td>Exacerbates ADT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Steroid side effects</td>
</tr>
<tr>
<td>enzalutamide</td>
<td>seizure history?</td>
<td>Exacerbates ADT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lowers seizure threshold</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td>sipuleucel-T*</td>
<td>Slowly growing disease</td>
<td>Minimal</td>
</tr>
<tr>
<td></td>
<td>Minimally symptomatic</td>
<td>Has little/no effect on PFS</td>
</tr>
<tr>
<td>Radium-223*</td>
<td>Pain requiring analgesics</td>
<td>?nausea, vomiting, anorexia, fatigue</td>
</tr>
<tr>
<td></td>
<td>No visceral disease</td>
<td></td>
</tr>
<tr>
<td>docetaxel</td>
<td>adequate hematologic function</td>
<td>Hematologic</td>
</tr>
<tr>
<td></td>
<td>adequate performance status</td>
<td>Alopecia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td>cabazitaxel</td>
<td>adequate hematologic function</td>
<td>More toxicity, less neuropathy</td>
</tr>
<tr>
<td></td>
<td>adequate performance status</td>
<td>than docetaxel</td>
</tr>
</tbody>
</table>

*Can be given with abiraterone or enzalutamide safely though unknown if efficacy is equivalent in combination*
Strategies for treatment: an example

CRPC
- Seizure history or fatigue?
  - enzalutamide
  + abiraterone
- slow growing?
  + add sipuleucel-T
  - painful bone mets?
    + radium-223
    - chemo-eligible?
      + enzalutamide
      - neuropathy?
        + docetaxel
        - cabazitaxel

Order of therapy likely irrelevant

<table>
<thead>
<tr>
<th>study</th>
<th>≥ 50% PSA decline w/ secondary rx</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective, 560 pts</td>
<td>D -&gt; C -&gt; ART: 37.3 mo OS D -&gt; ART -&gt; C: 36.0 mo OS ART -&gt; D -&gt; C: 30.1 mo OS</td>
<td>No sig diff 1</td>
</tr>
<tr>
<td>Retrospective, 4070 pts network meta-analysis comparing D -&gt; C to D -&gt; enza to D -&gt; abi to D -&gt; Rad-223</td>
<td>No significant difference in OS</td>
<td>2</td>
</tr>
</tbody>
</table>

D = docetaxel, C = cabazitaxel, ART = abiraterone or enzalutamide, abi = abiraterone, enza = enzalutamide, Rad-223 = radium-223

### Benefit of additional therapies decreases

<table>
<thead>
<tr>
<th>study</th>
<th>n</th>
<th>≥ 50% PSA decline w/ secondary rx</th>
<th>PFS (1st line)</th>
<th>PFS (2nd line)</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>D -&gt; abi -&gt; enza</td>
<td>35</td>
<td>abi-responsive: 43.8%</td>
<td>9 mo</td>
<td>4.9 mo</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>abi-unresponsive: 15.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abi -&gt; enza or enza -&gt; abi</td>
<td>126</td>
<td>1st line-responsive: 20%</td>
<td>3.6 mo</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st line-unresponsive: 25%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>enza -&gt; abi</td>
<td>30</td>
<td>10% overall</td>
<td>41 wks</td>
<td>15.4 wks</td>
<td>3</td>
</tr>
<tr>
<td>abi -&gt; D</td>
<td>35</td>
<td>26%</td>
<td>4.6 mo</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>abi -&gt; D vs D alone</td>
<td>24</td>
<td>abi -&gt; D: 38%</td>
<td>4.4 mo</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>95</td>
<td>D alone: 63%</td>
<td>7.6 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-&gt; abi/enza -&gt; Cab</td>
<td>41</td>
<td>39%</td>
<td>4.6 mo</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>response to D in mCRPC pts who initially received ADT alone vs ADT + D</td>
<td>68</td>
<td>ADT alone: 34%</td>
<td>7 mo</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>ADT+D: 17%</td>
<td>4.1 mo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

D = docetaxel, abi = abiraterone acetate, enza = enzalutamide, ADT = androgen deprivation therapy


### Talk outline

- Biology of metastatic prostate cancer
- Currently used agents
- Sequencing of agents
- **Novel agents and strategies**
DNA repair defects: Olaparib in pre-treated mCRPC

- Olaparib monotherapy in heavily pretreated CRPC
- Olaparib is a PARP inhibitor
- 16/49 pts had response (33%)
- Response =
  - RECIST
  - PSA 50% decline
  - Decrease in CTCs
- Veliparib has also been studied (Feng et al, ESMO 2016, Abstract #730PD)

<table>
<thead>
<tr>
<th>DNA repair defect</th>
<th>n</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>33</td>
<td>6.1%</td>
</tr>
<tr>
<td>+</td>
<td>16</td>
<td>87.5%</td>
</tr>
</tbody>
</table>

Mateo et al, NEJM 2015

Tumor evasion of enz/abi: splicing

the AR-V7 splice mutant

LBD = ligand binding domain  DBD = DNA binding domain  ARE = androgen response element
AR-V7: effects on abiraterone/enzalutamide

- Clinical study of AR-V7 testing:
  - tumor cells circulating in peripheral blood were tested for presence of AR-V7
  - if any AR-V7 RNA present, almost no response

Androgen receptor (AR) mutants

<table>
<thead>
<tr>
<th>mutation</th>
<th>Activated by:</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>L702H</td>
<td>glucocorticoids</td>
<td>1</td>
</tr>
<tr>
<td>V715M</td>
<td>Adrenal androgens (DHEA, androstenedione) and progesterone</td>
<td>2</td>
</tr>
<tr>
<td>H874Y</td>
<td>estradiol and progesterone</td>
<td>3</td>
</tr>
<tr>
<td>F876L</td>
<td>enzalutamide</td>
<td>4</td>
</tr>
<tr>
<td>T877A, T877S</td>
<td>estradiol and progesterone</td>
<td>3</td>
</tr>
<tr>
<td>T878A</td>
<td>Progesterone (3/18 pts who progressed on abi have mut)</td>
<td>5</td>
</tr>
</tbody>
</table>

**Variant Prostate Cancer**

Features:
- Non-adenocarcinoma histology
- Exclusively visceral metastases
- Lytic bone lesions
- Bulky lymphadenopathy
- Low PSA
- Evidence of neuroendocrine differentiation
  - Synaptophysin
  - Chromogranin A
  - Malignant hypercalcemia
  - CEA
- Short time to androgen independence

Treatment:
- Platinum-containing combinations:
  - Carboplatin/docetaxel
  - Cisplatin/etoposide

Aparicio et al., Clin Cancer Res, 2013
Conclusions

• Many agents now exist for mCRPC
• Order of use not defined
• Order agents on clinical symptoms and side effect profiles
• Molecular testing can be used to differentiate best therapies