New Concept of Anti-androgen Treatment for Castration-Resistant Prostate Cancer (CRPC)

Hyo Jin Lee, MD, PhD

Division of Hematology/Oncology, Department of Internal Medicine, Chungnam National University Hospital
Prostate Cancer

- Most common amongst men in the USA
- 2nd most common malignant cause of male death worldwide
- The life time risk of having microscopic evidence of prostate cancer for a 50 year old man is 42%

Global Health Problem
Stage Distribution & 5YSR, US, 2001-2007

Stage distribution (%) at diagnosis

Survival (%)
Current Landscape for Systemic Therapy in Castration-Resistant Prostate Cancer

**Disease Phenotype**

- Asymptomatic or minimally symptomatic
- Symptomatic
  - Pre-Doc
  - With Doc
  - Post-Doc

**2nd hormonal therapy**
- Sipuleucel-T (2010)
- Docetaxel (2004)
- Mitoxantrone (1996)
- Cabazitaxel (2010)
- Abiraterone (2011)
- MDV3100 (2012 ?)

**Surgical or medical castration**

Androgen Action in Prostate Cells

Hypothalamus

- LHRH

Ant. Pituitary

- ACTH
- LH

Adrenal Gland

Testis

- Androgen

Prostate

Androgen & AR signaling

- Main Oncogenic Driver
- Therapeutic Target

T, testosterone, SHBG, sex hormone-binding globulin, 5αR, 5α-reductase, DHT, dehydrotestosterone, AR, androgen receptor, HRE hormone-responsive element

Androgen Deprivation Therapy (ADT)

Hypothalamus → LHRH → Ant. Pituitary → ACTH, LH → Adrenal Gland, Testis → Androgen → Prostate

- LHRH analogue
- LHRH antagonist

Orchiectomy

Anti-androgen
Surgical Castration as an ADT

Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

Cancer Res 1941
Lutenising Hormone-Releasing Hormone Analogues (LHRHα)

Structure of LHRH

<table>
<thead>
<tr>
<th>LHRH analogue</th>
<th>Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buserelin</td>
<td>Glu-His-Trp-Ser-Tyr-D-Ser-Leu-Arg-Pro-Ethylamide</td>
</tr>
<tr>
<td>Leuprolide</td>
<td>Glu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-Ethylamide</td>
</tr>
<tr>
<td>Goserelin</td>
<td>Glu-His-Trp-Ser-Tyr-D-Ser-Leu-Arg-Pro-Az-Gly-NH₂</td>
</tr>
</tbody>
</table>

LHRH analogue
- Increased life span
- Increased affinity for receptor
- 100 times more potent
- A flare period at initial administration ➔ need co-administration of anti-androgen

Anti-Androgens (AAs)

- Bind to the androgen receptor in a competitive fashion
- Steroidal anti-androgen
  ![Cyproterone Acetate](image)
- Non-steroidal anti-androgen
  ![Bicalutamide](image)
  ![Flutamide](image)
  ![Nilutamide](image)
Androgen Deprivation Therapy (ADT)

- Surgical castration
  - Bilateral orchiectomy

- Chemical castration
  - LHRH agonist
  - LHRH antagonist

- Anti-androgen monotherapy

- Combined androgen blockade (CAB)
  - Castration plus anti-androgen

- Triple androgen blockade
  - Castration + anti-androgen + 5α reductase inhibitor
Androgen-Independent Prostate Cancer (?)

Androgen-dependent PCa
- Androgen deprivation therapy

Androgen-independent PCa
- 2nd line hormonal therapy, chemotherapy

New Mechanism of Castration Resistance

Increased Expression of Genes Converting Adrenal Androgens to Testosterone in Androgen-Independent Prostate Cancer

Michael Stanbrough,¹ Glenn J. Bubley,¹ Kenneth Ross,⁵ Todd R. Golub,² Mark A. Rubin,⁴ Trevor M. Penning,⁶ Phillip G. Febbo,³ and Steven P. Balk¹

[Diagram showing metabolic pathways involving DHEA, HSD3B2, AKR1C3, 3α-diol glucuronide, UGTB15, 3α-diol UGTB17, 3α-diol AKR1C2, 3α-diol AKR1C1, 3β-diol SRD5A1, 3β-diol SRD5A2, androstenedione, testosterone, and DHT.]

A. AKR1C3
B. AKR1C3
C. AKR1C2
D. AKR1C2

New Mechanism of Castration Resistance

Maintenance of Intratumoral Androgens in Metastatic Prostate Cancer: A Mechanism for Castration-Resistant Tumor Tumor Growth

New Strategies in CRPC-Targeting Persistent Dependency on Androgen and AR Signaling


Testosterone and DHT are produced in CRPC tissues from adrenal androgens or via de novo route.
Abiraterone Acetate (AA) in CRPC

Novel Steroidal Inhibitors of Human Cytochrome P450_{17\alpha} (17\alpha-Hydroxy-lyase-C_{17,20-lyase}): Potential Agents for the Treatment of Prostatic Cancer

Gerard A. Potter, † S. Elaine Barrie, Michael Jarman,* and Martin G. Rowlands

**Table 1. Enzyme Inhibition Data**

<table>
<thead>
<tr>
<th>compound</th>
<th>IC_{50} (nM)^a</th>
<th>C_{17,20-lyase}</th>
<th>17\alpha-hydroxylase</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>17</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.9</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5.6</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>76</td>
<td>270</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1000</td>
<td>4000</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>&gt;10 000</td>
<td>&gt;10 000</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>&gt;10 000</td>
<td>&gt;10 000</td>
<td></td>
</tr>
<tr>
<td>18(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ketoconazole</td>
<td>26</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>

**Figure**

Abiraterone Acetate (AA) in CRPC

- **Phase I trial (n=21)**
  - CRPC resistant to multiple hormonal therapies
  - AA, 250 to 2,000 mg (1,000 mg selected because of a plateau in PD)
  - PSA decline [≥ 30% (66%), ≥ 50% (57%), ≥ 90% (29%)]

Before and after AA treatment (6 months)
Phase III study of Abiraterone Acetate in CRPC (COU-AA-301)

N=1,195
Eligibility Criteria
- mCRPC
- Progression during or after docetaxel-based Tx
Stratification factor
- ECOG 0,1 vs. 2
- Prior CTX 1 vs. 2
April 2008 -

Randomization
1
Placebo
+ Prednisone
N= 398

2
Abiraterone
1,000 mg daily
+ Prednisone
5 mg x 2, daily
N= 797

Primary Outcome
OS
TTPP
PSA RR
rPFS
Median F/U (12.8 mos)

TTPP, time to PSA progression; rPFS, radiographic PFS
Unblinded following the 1st interim analysis on Aug 20, 2010

Overall survival

HR = 0.646 (0.54-0.77)  P < 0.0001

Abiraterone acetate:
14.8 months (95% CI: 14.1, 15.4)

Placebo:
10.9 months (95% CI: 10.2, 12.0)

2 Prior Chemo OS:
14.0 mos AA vs 10.3 mos placebo

1 Prior Chemo OS
15.4 mos AA vs 11.5 mos placebo

Days from Randomization
Overall survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>All</td>
<td>1195</td>
<td>0.66</td>
<td>0.56-0.79</td>
</tr>
<tr>
<td>Baseline ECOG</td>
<td>0-1</td>
<td>1068</td>
<td>0.64</td>
<td>0.53-0.78</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>127</td>
<td>0.81</td>
<td>0.53-1.24</td>
</tr>
<tr>
<td>Baseline BPI</td>
<td>&lt; 4</td>
<td>659</td>
<td>0.64</td>
<td>0.50-0.82</td>
</tr>
<tr>
<td></td>
<td>≥ 4</td>
<td>536</td>
<td>0.68</td>
<td>0.53-0.85</td>
</tr>
<tr>
<td>No. of prior chemo regimens</td>
<td>1</td>
<td>833</td>
<td>0.63</td>
<td>0.51-0.78</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>362</td>
<td>0.74</td>
<td>0.55-0.99</td>
</tr>
<tr>
<td>Type of progression</td>
<td>PSA only</td>
<td>363</td>
<td>0.59</td>
<td>0.42-0.82</td>
</tr>
<tr>
<td></td>
<td>Radiographic</td>
<td>832</td>
<td>0.69</td>
<td>0.56-0.84</td>
</tr>
<tr>
<td>Baseline PSA above median</td>
<td>YES</td>
<td>591</td>
<td>0.65</td>
<td>0.52-0.81</td>
</tr>
<tr>
<td>Visceral disease at entry</td>
<td>YES</td>
<td>709</td>
<td>0.60</td>
<td>0.48-0.74</td>
</tr>
<tr>
<td>Baseline LDH above median</td>
<td>YES</td>
<td>581</td>
<td>0.71</td>
<td>0.58-0.88</td>
</tr>
<tr>
<td>Baseline ALK-P above median</td>
<td>YES</td>
<td>587</td>
<td>0.60</td>
<td>0.48-0.74</td>
</tr>
<tr>
<td>Region</td>
<td>North America</td>
<td>652</td>
<td>0.64</td>
<td>0.51-0.80</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>543</td>
<td>0.69</td>
<td>0.54-0.90</td>
</tr>
</tbody>
</table>
## Efficacy

<table>
<thead>
<tr>
<th></th>
<th>AA (n = 797)</th>
<th>Placebo (n = 398)</th>
<th>HR 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTPP (months)</td>
<td>10.2</td>
<td>6.6</td>
<td>0.58 (0.46, 0.73)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>rPFS (months)</td>
<td>5.6</td>
<td>3.6</td>
<td>0.67 (0.59, 0.78)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PSA response rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>38.0%</td>
<td>10.1%</td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Confirmed</td>
<td>29.1%</td>
<td>5.5%</td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

TTPP, time to PSA progression; rPFS, radiographic PFS
Second-generation Antiandrogen in CRPC

Molecular determinants of resistance to antiandrogen therapy

Charlie D Chen¹,⁵,⁸, Derek S Welsbie³,⁵,⁸, Chris Tran¹,⁴, Sung Hee Baek⁴,⁶, Randy Chen¹, Robert Vessella⁷, Michael G Rosenfeld⁴,⁶ & Charles L Sawyers¹–⁵

Using microarray-based profiling of isogenic prostate cancer xenograft models, we found that a modest increase in androgen receptor mRNA was the only change consistently associated with the development of resistance to antiandrogen therapy. This increase in androgen receptor mRNA and protein was both necessary and sufficient to convert prostate cancer growth from a hormone-sensitive to a hormone-refractory stage, and was dependent on a functional ligand-binding domain. Androgen receptor antagonists showed agonistic activity in cells with increased androgen receptor levels; this antagonist-agonist conversion was associated with alterations in the recruitment of coactivators and corepressors to the promoters of androgen receptor target genes. Increased levels of androgen receptor confer resistance to antiandrogens by amplifying signal output from low levels of residual ligand, and by altering the normal response to antagonists. These findings provide insight toward the design of new antiandrogens.

Second-generation Antiandrogen in CRPC

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


Science 2009
MDV3100 in CRPC

**Phase I-II trial (n=140)**
- Patients with progressive CRPC
- MDV3100, 30 to 600 mg

- PSA response ($\geq 50\%$) - 56%
- Soft tissue response - 22%
- Time to radiologic progression - 47 weeks
Phase III study of MDV3100 in CRPC (AFFIRM trial)

N=1,199

Eligibility Criteria
- mCRPC
- Progression after docetaxel-based Tx

Stratification factor
- ECOG 0,1 vs. 2
- Mean BPI score

Sept 2009 ~ Nov 2010

Randomization

1. Placebo
   - N= 399

2. MDV3100 160 mg daily
   - N= 797

Primary Outcome
- OS
- PSA-R
- Soft tissue-R
- QoL-R
- rPFS
- TTPP
- CTC

Median F/U (14.4 mos)

R, response; QoL, quality of life; rPFS, radiographic PFS; TTPP, time to PSA progression; CTC, circulating tumor cells

Unblinded following the planned interim analysis (Sept 25, 2011)
Overall survival

HR = 0.631 (0.529, 0.752) \( P < 0.0001 \)
37% Reduction in Risk of Death

MDV3100: 18.4 months
(95% CI: 17.3, NYR)

Placebo: 13.6 months
(95% CI: 11.3, 15.8)
Overall survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio for Death (95% CI)</th>
<th>Overall Survival Median (mo) MDV3100/Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>0.63 (0.53–0.75)</td>
<td>18.4 / 13.6</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>0.63 (0.46–0.87)</td>
<td>— / 12.4</td>
</tr>
<tr>
<td>≥65</td>
<td>0.63 (0.51–0.78)</td>
<td>18.4 / 13.9</td>
</tr>
<tr>
<td>Baseline ECOG Performance Status Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>0.62 (0.52–0.75)</td>
<td>— / 14.2</td>
</tr>
<tr>
<td>2</td>
<td>0.65 (0.39–1.07)</td>
<td>10.5 / 7.2</td>
</tr>
<tr>
<td>Baseline Mean Pain Score on BPI-SF (Question #3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>0.59 (0.47–0.74)</td>
<td>— / 16.2</td>
</tr>
<tr>
<td>≥4</td>
<td>0.71 (0.54–0.94)</td>
<td>12.4 / 9.1</td>
</tr>
<tr>
<td>Geographic Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>0.63 (0.47–0.83)</td>
<td>17.4 / 12.3</td>
</tr>
<tr>
<td>Other</td>
<td>0.64 (0.51–0.80)</td>
<td>— / 14.4</td>
</tr>
<tr>
<td>Number of Prior Chemotherapy Regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.59 (0.48–0.73)</td>
<td>— / 14.2</td>
</tr>
<tr>
<td>≥2</td>
<td>0.74 (0.54–1.03)</td>
<td>15.9 / 12.3</td>
</tr>
<tr>
<td>Type of Progression at Study Entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA Progression Only</td>
<td>0.62 (0.46–0.83)</td>
<td>— / 19.5</td>
</tr>
<tr>
<td>Radiographic Progression ± PSA Progression</td>
<td>0.64 (0.52–0.80)</td>
<td>17.3 / 13.0</td>
</tr>
<tr>
<td>Baseline value &gt;Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>0.62 (0.50–0.78)</td>
<td>15.3 / 10.3</td>
</tr>
<tr>
<td>LDH</td>
<td>0.61 (0.50–0.76)</td>
<td>12.4 / 8.5</td>
</tr>
</tbody>
</table>
## Efficacy

<table>
<thead>
<tr>
<th>Response</th>
<th>MDV3100</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed PSA Decline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50% from Baseline</td>
<td>54.0%</td>
<td>1.5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ 90% from Baseline</td>
<td>24.8%</td>
<td>0.9%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Soft Tissue Response by CT/MRI Imaging</td>
<td>28.9%</td>
<td>3.8%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression</th>
<th>MDV3100</th>
<th>Placebo</th>
<th>Hazard Ratio (Confidence Interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time to PSA Progression (months)</td>
<td>8.3</td>
<td>3.0</td>
<td>0.248 (0.204, 0.303)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median Radiographic Progression-free Survival (months)</td>
<td>8.3</td>
<td>2.9</td>
<td>0.404 (0.350, 0.466)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
**Current Landscape for Systemic Therapy in Castration-Resistant Prostate Cancer**

**Disease Phenotype**

- **Asymptomatic or minimally symptomatic**
  - Pre-Doc
  - With Doc
  - Post-Doc

- **Symptomatic**
  - 2nd hormonal therapy
    - Sipuleucel-T (2010)
  - Docetaxel (2004)
  - Mitoxantrone (1996)
  - Cabazitaxel (2010)
  - Abiraterone (2011)
  - MDV3100 (2012 ?)

**Surgical or medical castration**

Phase III study of Abiraterone Acetate in CRPC (COU-AA-302)

N=1,088

Eligibility Criteria
- mCRPC
- chemo-naïve
- asymptomatic or mildly symptomatic

Stratification factor
- ECOG 0,1 vs. 2

1Q2010 -

Abiraterone 1,000 mg daily + Prednisone 5 mg x 2, daily
N= 546

Placebo + Prednisone
N= 542

Primary Outcome
rPFS/OS
- Time to opiate use
- Time to chemotherapy
- Time to PS deterioration
TTPP
- Median F/U (22.3 mos)

rPFS, radiographic PFS; TTPP, time to PSA progression

Ryan et al. ASCO 2012
Progression-Free Survival

Ryan et al. ASCO 2012

AA + P (median, mos): NR
PL + P (median, mos): 8.3
HR (95% CI): 0.43 (0.35-0.52)
P value: < 0.0001
## Progression-Free Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>Median (months)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>ALL</td>
<td>NE 8.3</td>
<td>0.43</td>
<td>(0.35-0.52)</td>
</tr>
<tr>
<td>Baseline ECOG</td>
<td>0</td>
<td>13.7</td>
<td>0.45</td>
<td>(0.36-0.57)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>NE 7.4</td>
<td>0.35</td>
<td>(0.23-0.54)</td>
</tr>
<tr>
<td>Baseline BPI</td>
<td>0-1</td>
<td>NE 8.4</td>
<td>0.42</td>
<td>(0.32-0.54)</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>11.1</td>
<td>0.51</td>
<td>(0.35-0.75)</td>
</tr>
<tr>
<td>Bone metastasis only at entry</td>
<td>YES</td>
<td>NE 13.7</td>
<td>0.48</td>
<td>(0.34-0.69)</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>11.3</td>
<td>0.38</td>
<td>(0.30-0.49)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 65</td>
<td>13.7</td>
<td>0.36</td>
<td>(0.25-0.53)</td>
</tr>
<tr>
<td></td>
<td>≥ 65</td>
<td>9.7</td>
<td>0.45</td>
<td>(0.35-0.58)</td>
</tr>
<tr>
<td></td>
<td>≥ 75</td>
<td>NE 11.0</td>
<td>0.57</td>
<td>(0.39-0.83)</td>
</tr>
<tr>
<td>Baseline PSA above median</td>
<td>YES</td>
<td>11.9</td>
<td>0.44</td>
<td>(0.33-0.58)</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>NE 8.5</td>
<td>0.40</td>
<td>(0.29-0.54)</td>
</tr>
<tr>
<td>Baseline LDH above median</td>
<td>YES</td>
<td>NE 5.6</td>
<td>0.37</td>
<td>(0.28-0.49)</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>NE 9.0</td>
<td>0.48</td>
<td>(0.36-0.65)</td>
</tr>
<tr>
<td>Baseline ALK-P above median</td>
<td>YES</td>
<td>11.5</td>
<td>0.50</td>
<td>(0.38-0.66)</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>NE 8.3</td>
<td>0.34</td>
<td>(0.26-0.47)</td>
</tr>
<tr>
<td>Region</td>
<td>N.A.</td>
<td>NE 8.2</td>
<td>0.36</td>
<td>(0.27-0.48)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>11.5</td>
<td>0.52</td>
<td>(0.39-0.69)</td>
</tr>
</tbody>
</table>

Ryan et al. ASCO 2012
Overall Survival

- AA + P (median, mos): NR
- PL + P (median, mos): 27.2
- HR (95% CI): 0.75 (0.61-0.93)
- P value: 0.0097
## Secondary End Points

<table>
<thead>
<tr>
<th></th>
<th>AA + P</th>
<th>Placebo + P</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to opiate use</strong></td>
<td>NR</td>
<td>23.7</td>
<td>0.69 (0.57, 0.83)</td>
<td>0.0001</td>
</tr>
<tr>
<td>(cancer related pain)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time to chemotherapy initiation</strong></td>
<td>25.2</td>
<td>16.8</td>
<td>0.58 (0.49, 0.69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Time to ECOG PS deterioration</strong></td>
<td>12.3</td>
<td>10.9</td>
<td>0.82 (0.71, 0.94)</td>
<td>0.0053</td>
</tr>
<tr>
<td><strong>Time to PSA progression</strong></td>
<td>11.1</td>
<td>5.6</td>
<td>0.49 (0.42, 0.57)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Note: All secondary end points remain significant after adjusting for multiplicity testing

Patient Reported Outcomes favored AA +P vs. Placebo +P
Full data to be reported

Ryan et al. ASCO 2012
Conclusions

A better understanding of tumor biology implicated in CRPC provides new room to further suppress androgenic stimulation of prostate cancer

Abiraterone acetate and MDV3100 developed on the basis of this science show big advances

Large gaps in our knowledge and understanding of CRPC persist, and a major effort is needed to exploit the full potential of these agents.
In your opinion, which of the following is the best treatment option in patients with metastatic prostate cancer?

1. Bilateral orchiectomy
2. LHRH agonist ± anti-androgen of at least 7 days
3. LHRH agonist + anti-androgen
4. LHRH antagonist
Which of the following is the standard treatment of symptomatic patients with castration-resistant prostate cancer?

1. Ketoconazole
2. Anti-androgen withdrawal
3. Mitoxantrone-based chemotherapy
4. Docetaxel-based chemotherapy
5. Abiraterone acetate
In your opinion, which of the following is the best treatment option in CRPC patients who have failed docetaxel-based chemotherapy?

1. Mitoxantrone-based chemotherapy
2. Docetaxel rechallenge
3. Cabazitaxel-based chemotherapy
4. Abiraterone acetate
5. MDV3100
Thanks for your attention !!!