Novel Hormonal Therapy for Castration Resistant Prostate Cancer

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Disclosures

- Research support or honoraria:
  - Cougar Biotech, J&J, Medivation,
  - Astellas, Sanofi-Aventis
Time-line for prostate cancer therapeutics

- Huggins* Castration 1940-1950
- Orchietomy DES 1960-1980
- Shally* LHRH agonists 1977-1990
- Flutamide 1989
- Nilutamide 1997
- Bicalutamide 1999
- Mitoxantrone, Docetaxel, Zoledronic acid 2002-2004
- Degerelix

* Nobel Prize in 1966
Treatment options for patients with CRPC


- Zoledronic Acid\(^1\)
- Docetaxel\(^2\)
- Cabazitaxel\(^4\)
- Denosumab\(^5\)
- Sipuleucel-T\(^3\)
- Abiraterone\(^6\)
- MDV3100\(^7\)
- Alpharadin\(^8\)

\(^1\) Saad et al. J Natl Cancer Inst 2002; 94: 1458–1468
\(^4\) de Bono et al. Lancet. 2010; 376(9747): 1147-1154
\(^5\) Fizazi et al. Lancet 2011; 377(9768): 813-822
\(^8\) Parker C. et al. ESMO 2011: Abstract 2, and ASCO GU 2012
Prostate Cancer Clinical States

**Noncastrate**
Diagnoses: 217,730

- Clinically Localized Disease
- Rising PSA
- Clinical Metastases: Noncastrate
- Rising PSA: Castrate

**Castration resistant**
Deaths: 32,050

- Clinical Metastases: Castrate Pre-Provenge
- Clinical Metastases: Castrate 1st-Line Docetaxel
- Clinical Metastases: Castrate Post-Cabazitaxel Abiraterone MDV3011 Radium 223

With detectable metastases: deaths from cancer exceed those from other causes

Challenges to Developing New Drugs for Advanced Prostate Cancer
Bone Flare with PSA Decline

Challenges to Developing New Drugs for Advanced Prostate Cancer

- OS preferred outcome measure
- Lack of surrogate markers
- Inter-patient molecular heterogeneity
- PCWG2* (Prostate Working Group Guidelines 2)

Fall in Circulating Tumor Cells (CTC) Count ( >5 to <5 ) Associated With Improved OS

median OS in

Group Description N (%) Months (95% CI)
1 <5 CTC at all draws 88 (38) 26 (21.4 to ------)
2 >5 CTC at BL & <5 CTC at last draw 45 (20) 21.3 (18.4 to ------)
3 <5 CTC at early draw & >5 CTC at last draw 26 (11) 9 9.3 (8.2 to 11.3)
4 >5 CTC at all draws 71 (31) 6.8 (5.8 to 10.3)

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

*P-values not adjusted for multiple hypothesis tests.
Targeting the Androgen Receptor (AR)
AR Signaling Pathways

Ligand dependent

- Estrogens
- Progestins
- Glucocorticoids
- Antiandrogens
- MutAR
- Cofactor Molecules

Ligand independent

- Cytokines, Oncogenes
- Growth factors
- Intracellular kinase cascade
- AR interaction/Phosphorylation
- AR synthesis
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 Eitetsu Koh,1 Hiroshi Fujita,1 Yuji Maeda,1 Masayuki Egawa,1 Kiyoshi Koshida,1

Vol. 10, 440-448, January 15, 2004

Clinical Cancer Research

Featured Article

The Androgen Axis in Recurrent Prostate Cancer

James L. Mohler,1,2,6,7,8 Christopher W. Gregory,2,5 O. Harris Ford III,1,6 Desok Kim,1 Catharina M. Weaver,3 Peter Petrusz,4 Elizabeth M. Wilson,3,5,6 and Frank S. French2,6

Departments of 1Surgery (Division of Urology), 2Pathology and Laboratory Medicine, 3Pediatrics (Laboratories for Reproductive Biology), 4Cell and Developmental Biology, and 5Biochemistry and Biophysics, and 6University of North Carolina-Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina; 7Department of Urology, State University of New York at Buffalo; and 8Department of Urologic Oncology, Roswell Park Cancer Center, Buffalo, New York.

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,2 Colleen C. Nelson,6 Alvin M. Matsumoto,2,5 William J. Bremner,2 Martin E. Gleave,6 and Peter S. Nelson1
New Generation Anti Androgens

**Abiraterone Acetate (Phase 3 studies post- and pre-docetaxel)**
- Potent and selective inhibitor of CYP17-α-hydroxylase and C17,20-lyase

**MDV3100 (Phase 3 studies post- and pre-docetaxel)**
- AR antagonist, inhibits nuclear translocation and blocks DNA binding of the receptor and activation

**TAK-700 (Phase 3 studies post- and pre-docetaxel)**
- Selective, nonsteroidal, small-molecule inhibitor of C17,20-lyase

**TOK-001 (Phase 1/2 ARMOR 1)**
- AR antagonist, and AR degrader, and a CYP17 lyase inhibitor

**SARDS (AZD3514)**
- Selective androgen receptor degraders (destroy the AR receptor)

**ARN-509 (Phase 1/2)**
- AR antagonist, inhibits nuclear translocation and DNA binding of the receptor

**ODM-201 (Phase 1/2 Arcades Trial, ESMO LBA 25-PR)**
- AR antagonist, non steroidal
Abiraterone Acetate: Androgen Biosynthesis Inhibitor

Cholesterol → Pregnenolone → 17OH-Pregnenolone → DHEA → Androstenedione → Testosterone → DHT

From Ryan C et al, Clin Oncol 30, 2012 (suppl; abstr LBA4518)
Abiraterone Inhibits Androgen Biosynthesis Through CYP17

• Androgens produced at 3 critical sites
  – Testes
  – Adrenal gland
  – Prostate tumor cells

• Abiraterone inhibits biosynthesis of androgens that stimulate tumor cell growth

• PSA and radiographic responses in Phase 2 studies of CRPC
  – Chemo-naïve and post-chemo patients\(^1\)-\(^6\)

Abiraterone Acetate Phase III Post-Chemo Study Design

- **1195** patients progressive mCRPC
- Failed 1 or 2 chemotherapy regimens, 1 with docetaxel
- Phase 3 multicenter, randomized, double-blind, placebo-controlled study (147 sites in 13 countries; USA, Europe, Australia, Canada)
- **Stratification by:**
  - ECOG performance status 0-1 vs 2
  - Worst pain over previous 24 hours BPI short form; 0-3 (absent) vs 4-10 (present)
  - Prior chemotherapy 1 vs 2
  - Type of progression PSA only vs radiographic with or without PSA

Efficacy endpoints (ITT)
- **1° endpoint:**
  - OS (25% improvement; HR 0.8)
- **2nd endpoints:**
  - TTPP
  - rPFS
  - PSA response

- Placebo daily Prednisone 5 mg bid n = 398
- Abiraterone 1000 mg daily Prednisone 5 mg bid n = 797

Overall Survival: Second Pre-planned Analysis
Median benefit 4.6 months

HR = 0.74 (0.638-0.859) P<0.0001
26% reduction in risk of death

Placebo median OS (95% CI):
11.2 months (10.41-13.14)

AA median OS (95% CI):
15.8 months (14.82-17.02)

Median follow-up 20.2 months

Scher HI et al. J Clin Oncol 2011; 29 (suppl): LBA4517
Fizazi K et al, Lancet Oncol,( in press)
Survival Benefit Consistently Observed Across Patient Subgroups

<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 chemotherapy 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>Age, years</td>
<td>&lt; 65</td>
<td>832</td>
<td>0.66</td>
<td>0.48-0.91</td>
</tr>
<tr>
<td></td>
<td>≥ 65</td>
<td>362</td>
<td>0.67</td>
<td>0.55-0.82</td>
</tr>
<tr>
<td>Visceral disease at entry</td>
<td>Yes</td>
<td>353</td>
<td>0.70</td>
<td>0.52-0.94</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>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>N 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>

All Secondary End Points Achieved Statistical Significance

<table>
<thead>
<tr>
<th></th>
<th>Abiraterone</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival</td>
<td>15.8 mo</td>
<td>11.2 mo</td>
<td>0.74 (0.64 - 0.86)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Time to PSA progression</td>
<td>10.2 mo</td>
<td>6.6 mo</td>
<td>0.58 (0.46 - 0.73)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Radiographic PFS</td>
<td>5.6 mo</td>
<td>3.6 mo</td>
<td>0.67 (0.58 - 0.78)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PSA response rate</td>
<td>29%</td>
<td>6%</td>
<td>N/A</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Scher et al. J Clin Oncol 2011; 29 (suppl): Abstract LBA4517
Symptomatic Improvement

Pain Intensity Palliation (BPI questionnaire)


\[ P = 0.0002 \]

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients Experiencing Palliation</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>155/349</td>
<td>44.4%</td>
</tr>
<tr>
<td>Placebo</td>
<td>44/163</td>
<td>27.0%</td>
</tr>
</tbody>
</table>
Symptomatic Improvement
Pain Intensity Palliation Over Time


Patients not yet experiencing palliation

Placebo: 10.25 months
Abiraterone: 5.55 months

$P = 0.0010$ (log-rank)
## Summary of AEs

<table>
<thead>
<tr>
<th></th>
<th>AA (n = 791)</th>
<th>Placebo (n = 394)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grades 3/4</td>
</tr>
<tr>
<td>All treatment-emergent AEs</td>
<td>98.9%</td>
<td>54.5%</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>37.5%</td>
<td>32.1%</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>18.7%</td>
<td>10.5%</td>
</tr>
<tr>
<td>AEs leading to death</td>
<td>11.6%</td>
<td></td>
</tr>
<tr>
<td>Deaths within 30 days of last</td>
<td>10.5%</td>
<td></td>
</tr>
<tr>
<td>dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying disease</td>
<td>7.5%</td>
<td></td>
</tr>
<tr>
<td>Other specified cause</td>
<td>2.9%</td>
<td></td>
</tr>
</tbody>
</table>

### Adverse Events of Special Interest

<table>
<thead>
<tr>
<th></th>
<th>AA (n = 791)</th>
<th>Placebo (n = 394)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grades 3/4</td>
</tr>
<tr>
<td><strong>Fluid retention</strong></td>
<td>30.5%</td>
<td>2.3%</td>
</tr>
<tr>
<td><strong>Hypokalemia</strong></td>
<td>17.1%</td>
<td>3.8%</td>
</tr>
<tr>
<td><strong>LFT abnormalities</strong></td>
<td>10.4%</td>
<td>3.5%</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>9.7%</td>
<td>1.3%</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>13.3%</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

*aMost frequently reported cardiac terms were tachycardia and atrial fibrillation. The rate of grade 5 lethal cardiac events was identical in the 2 study arms: 1.3% (10 pts) in AA and 1.3% (5 pts) in placebo.*

**FDA-Approved April 11, 2011 and EMA September 7, 2011**
Higher conversion rates from unfavorable (≥5 CTC) to favorable (<5 CTC)

<table>
<thead>
<tr>
<th>Conversion status</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conversion</td>
<td>AA (n=272)</td>
<td>Placebo (n=150)</td>
<td>AA (n=245)</td>
</tr>
<tr>
<td>(n)</td>
<td>422</td>
<td></td>
<td>374</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.0001</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

p value from chi-square statistic

Scher et al. J Clin Oncol 2011; 29 (suppl): Abstract LBA4517
MDV3100 (Enzalutamide)

- Oral drug rationally designed to target AR signaling, impacting multiple steps in AR signaling pathway.

- No demonstrated agonist effects in pre-clinical models.

Patient Population: 1199 patients with progressive CRPC
*Failed docetaxel chemotherapy

Corticosteroids were not required, but allowed

Stratification: PS and BPI score, PCWG2 criteria used

156 centers from 15 countries and 5 continents
September 2009 - November 2010
Enzalutamide Overall Survival
Median benefit 4.8 months

HR = 0.631 (0.529, 0.752) P <0.0001
37% reduction in risk of death

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

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

## Survival Benefit Across All Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio for Death (95% CI)</th>
<th>Overall Survival median (mo) Enzalutamide / 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><strong>Age</strong></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><strong>Baseline ECOG Performance Status Score</strong></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><strong>Baseline Mean Pain Score on BPI-SF (Question #3)</strong></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><strong>Geographic Region</strong></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><strong>Number of Prior Chemotherapy Regimens</strong></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><strong>Type of Progression at Study Entry</strong></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><strong>Baseline value &gt;Median</strong></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>

*Favors Enzalutamide* | *Favors Placebo*

* *Dots are approximately proportional to MDV3100 population*

Enzalutamide: PSA Response Rates

HR = 0.688 (95% CI: 0.566, 0.835) P<0.0001
31% reduction in the time to first SRE

Enzalutamide: 16.7 months
(95% CI: 14.6, 19.1)

Placebo: 13.3 months
(95% CI: 9.9, NYR)

Sternberg CN et al. Global Can Prost, Brussels June 2012
### Adverse Events of Special Interest

<table>
<thead>
<tr>
<th>Event</th>
<th>All Grades</th>
<th>Grade ≥3 Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enzalutamide (n = 800)</td>
<td>Placebo (n = 399)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33.6%</td>
<td>29.1%</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>6.1%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td>LFT Abnormalities*</td>
<td>1.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Seizure</td>
<td>0.6%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

*Inchyperbilirubinemia, AST increased, ALT increased, LFT abnormal, transaminases increased, and blood bilirubin increased.

**FDA-Approved August 31, 2012**
**Table 2. ARN-509 and MDV3100 steady-state levels in plasma and brain tissue**

<table>
<thead>
<tr>
<th>Dose, mg/kg/d</th>
<th># mice</th>
<th>Plasma $C_{24h}$, $\mu$g/mL$^a$</th>
<th>Brain $C_{24h}$, $\mu$g/g$^a$</th>
<th>Brain:plasma (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARN-509</td>
<td>10</td>
<td>1.64 ± 0.30</td>
<td>0.479 ± 0.132</td>
<td>29.3 ± 6.3</td>
</tr>
<tr>
<td>MDV3100</td>
<td>5</td>
<td>10.5 ± 2.3</td>
<td>2.01 ± 0.83</td>
<td>18.8 ± 4.4</td>
</tr>
</tbody>
</table>

Note: ARN-509 and MDV3100 were measured in plasma or brain tissue following 28-day daily dosing at 10 mg/kg/d. Plasma and brain were isolated 24 hours after final dose on day 28. ARN-509 and MDV3100 levels quantified with an LC/MS/MS method.

$^a$mean ± SD.
Effect of ARN-509 on PSA in Phase I Study

Maximum PSA Decline (%) from Baseline

PSA decrease has been shown in 28 of 30 patients across all doses

Rathkopf DE et al, ASCO 2012
Clinical Need in CRPC Pre-Chemotherapy

- An intervention with little toxicity compared to chemotherapy for asymptomatic or mildly symptomatic CRPC patients

- Aim to prevent or delay the onset of pain related to metastatic disease and disease progression

- Prolong survival
Pre - Chemotherapy Trials in CRPC

- Abiraterone
- PREVAIL
- TAK-700
Overall Study Design of COU-AA-302

Patients
- Progressive chemo-naïve mCRPC patients (Planned N = 1088)
- Asymptomatic or mildly symptomatic

Efficacy end points
Co-Primary:
- rPFS by central review
- OS
Secondary:
- Time to opiate use (cancer-related pain)
- Time to initiation of chemotherapy
- Time to ECOG-PS deterioration
- TTPP

1:1 RANDOMIZED

AA 1000 mg daily Prednisone 5 mg BID (Actual n = 546)

Placebo daily Prednisone 5 mg BID (Actual n = 542)

• Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada
• Stratification by ECOG performance status 0 vs 1

Ryan C et al, Clin Oncol 30, 2012 (suppl; abstr LBA4518)
## COU-AA-302 Statistical Plan

<table>
<thead>
<tr>
<th>Overall Assumption</th>
<th>rPFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Power</td>
<td>91%</td>
<td>85%</td>
</tr>
<tr>
<td>HR</td>
<td>0.67</td>
<td>0.80</td>
</tr>
<tr>
<td>Expected events</td>
<td>378</td>
<td>773</td>
</tr>
</tbody>
</table>

### Planned OS Analysis

<table>
<thead>
<tr>
<th>Quarter</th>
<th>IA1 (116 Events, $\alpha &lt; 0.0001$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1</td>
<td>(~15% OS Events)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quarter</th>
<th>IA2 (311 Events, $\alpha = 0.0005$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA2</td>
<td>(40% OS Events)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quarter</th>
<th>IA3 (425 Events, $\alpha = 0.0034$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA3</td>
<td>(55% OS events)</td>
</tr>
</tbody>
</table>

IA = interim analysis. $H_0$, HR=1.0.

Ryan C et al, Clin Oncol 30, 2012 (suppl; abstr LBA4518)
Significant Improvement in Radiologic PFS Primary End Point (IDMC)

Progression-Free (%)

Time to Progression or Death (Months)

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

Data cutoff 12/20/2010.
NR, not reached; PL, placebo.
Strong Trend in OS Primary End Point

Survival (%) vs. Time to Death (Months)

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

Data cutoff 12/20/2011.
Pre-specified significance level by O'Brien-Fleming Boundary = 0.0008.

Ryan C et al, Clin Oncol 30, 2012 (suppl; abstr LBA4518)
## Point Estimates for OS Favor Abiraterone in all Patient Subgroups

<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></td>
<td></td>
<td>AA</td>
<td>Placebo</td>
<td>Favors AA</td>
</tr>
<tr>
<td>All subjects</td>
<td>ALL</td>
<td>NE</td>
<td>27.2</td>
<td>NE</td>
</tr>
<tr>
<td>Baseline ECOG</td>
<td>0</td>
<td>NE</td>
<td>27.2</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>NE</td>
<td>26.4</td>
<td>NE</td>
</tr>
<tr>
<td>Baseline BPI</td>
<td>0-1</td>
<td>NE</td>
<td>27.2</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>25.5</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Bone metastasis only at entry</td>
<td>YES</td>
<td>NE</td>
<td>27.2</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>NE</td>
<td>27.5</td>
<td>NE</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 65</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>≥ 65</td>
<td>NE</td>
<td>26.4</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>≥ 75</td>
<td>NE</td>
<td>23.8</td>
<td>NE</td>
</tr>
<tr>
<td>Baseline PSA above median</td>
<td>YES</td>
<td>26.9</td>
<td>23.8</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Baseline LDH above median</td>
<td>YES</td>
<td>NE</td>
<td>23.6</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>NE</td>
<td>27.5</td>
<td>NE</td>
</tr>
<tr>
<td>Baseline ALK-P above median</td>
<td>YES</td>
<td>NE</td>
<td>23.6</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>NE</td>
<td>27.5</td>
<td>NE</td>
</tr>
<tr>
<td>Region</td>
<td>N.A.</td>
<td>NE</td>
<td>27.2</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>NE</td>
<td>NE</td>
<td></td>
</tr>
</tbody>
</table>

Ryan C et al, Clin Oncol 30, 2012 (suppl; abstr LBA4518)
Subsequent Therapy Was Common

<table>
<thead>
<tr>
<th></th>
<th>AA + P (n = 546) n (%)</th>
<th>Placebo + P (n = 542) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. with selected subsequent therapy for mCRPC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>207 (37.9)</td>
<td>287 (53.0)</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>45 (8.2)</td>
<td>52 (9.6)</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>39 (7.1)</td>
<td>63 (11.6)</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>27 (4.9)</td>
<td>24 (4.4)</td>
</tr>
<tr>
<td>Abiraterone acetate*</td>
<td>26 (4.8)</td>
<td>54 (10.0)</td>
</tr>
</tbody>
</table>

*Prior to unblinding (e.g. not per protocol)

Ryan C et al, Clin Oncol 30, 2012 (suppl; abstr LBA4518)
## Serologic and Clinical Responses

<table>
<thead>
<tr>
<th></th>
<th>AA + P (n = 546)</th>
<th>Placebo + P (n = 542)</th>
<th>RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA decline ≥50%</td>
<td>62%</td>
<td>24%</td>
<td>NA</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>N=220</td>
<td>N=218</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECIST: Defined objective response</td>
<td>36%</td>
<td>16%</td>
<td>2.273 (1.591, 3.247)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Complete response</td>
<td>11%</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>25%</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>61%</td>
<td>69%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2%</td>
<td>15%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ryan C et al, Clin Oncol 30, 2012 (suppl; abstr LBA4518)
Summary

- In patients with asymptomatic and mildly symptomatic, chemotherapy-naïve mCRPC, treatment with abiraterone acetate plus prednisone:
  - Delays disease progression
  - Increases survival
  - Extends time with minimal or no symptoms
  - No new important safety signals

Ryan C et al, Clin Oncol 30, 2012 (suppl; abstr LBA4518)
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
- Randomize 1:1
- MDV3100 160 mg QD
- Placebo QD
- 1° end point: OS and PFS
- 2° end point: time to 1st SRE, time to start cytotoxic chemotherapy

1st patient enrolled Sept 29, 2010
Closed to accrual in March 2012

www.clinicaltrials.gov NCT01212991

Beer T and Tombal B, co-PI
TAK 700 : Pre-Chemo Study
Bone scan flare up in patient with decrease PSA

Pre treatment : January 23 2012
PSA 80 mildly symptomatic

Week 13: April 14, 2012
PSA 49 asymptomatic
Around the world on TAK-700
Around the world on TAK-700
New Agents and Trials for CRPC

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

Docetaxel
- OGX-011
- Dasatinib
- Aflibercept

Post-docetaxel
- Abiraterone
- MDV3100
- Cabazitaxel
- Ipilimumab
- TAK-700
- Alpharadin
- Cabozantinib

7Parker C et al, ESMO LBA 2 and ASCO 2012, 8Ryan C et al, Clin Oncol 30, 2012 (suppl; abstr LBA4518)
Progress and Conclusions in mCRPC

• Unequivocal evidence of continued involvement of the AR signaling axis

• Non toxic hormonal therapies pre and post chemotherapy of interest

• Need to address prostate cancer heterogeneity to move the field forward

• Progress can be made if we understand mechanisms of response and resistance

• Need to evaluate the best sequence and combinations
Thank you for your attention