Abiraterone acetate: Targeting CYP17 to treat advanced prostate cancer

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The Institute of Cancer Research, and
The Royal Marsden Hospital

Paris March 2011
Hypothesis 2004:

- ‘Hormone Refractory’ prostate cancer was NOT hormone refractory but frequently remained driven by a ligand-activated androgen receptor (AR).

Attard, Belldegrun and de Bono; BJU, 2004
de Bono & Ashworth, Nature 2010
Evidence that AR is a hard habit to break

• Hormonal treatments continue to have antitumor activity
• High intratumoral androgens despite castration
  – Preclinical and clinical evidence of intracrine synthesis
• Castration resistance associated with:
  – AR amplification (increased gene dose)
  – AR mutations that increase AR (transcriptional) activity
  – ↑ AR(<2x) expression (ligand driven) in isogenic resistant lines
• Identification of oncogenic translocations/fusions driven by androgens + oestrogen response elements (ETS genes; TMPRSS2/ERG in 50-70% of PC)

Attard, Cooper and de Bono; Cancer Cell, 2009
ETS gene rearrangements in Prostate Cancer

Transcription of ERG becomes regulated by steroid receptors (ARE and ERE)

Class N
Class Edel
Class Esplit

Attard et al, Oncogene 2008; Attard et al Cancer Research 2009
Drug development strategies to target continued AR signaling

• Several strategies to target hormone driven AR
  – Target hormones driving AR signaling
    • Develop inhibitors of intracrine androgenic steroid synthesis
  – Better AR antagonists
    • Can we make a ‘pure’ antagonist (partial agonist effects)?*
  – Target AR chaperones by HSP90i; HDAC6i
  – Tubulin binding drugs!
A new ‘old’ drug for prostate cancer

- Drug discovered and made at ICR in 1990s
- First Phase I & II trials performed at RMH
- Results confirmed in multiple US trials
  - Memorial Sloan Kettering, MD Anderson, UCSF
- Abiraterone evaluated in Phase III trials
  - Bought by J&J for $1 billion; regulatory submissions
P450c17 inhibitors: Chemical development

Abiraterone

- 2-pyridyl
  - $\text{IC}_50$ (nm)
  - Lyase 76
  - Hydroxylase 270

- 3-pyridyl
  - $\text{IC}_50$ (nm)
  - Lyase 2.9
  - Hydroxylase 4

- 4-pyridyl
  - $\text{IC}_50$ (nm)
  - Lyase 1000
  - Hydroxylase 4000

Developed at The Institute of Cancer Research: Jarman M, Potter G, Barrie E
Mechanism of action of abiraterone

Pregnenolone → Deoxycorticosterone → Corticosterone → Aldosterone

17OH-Pregnenolone → 11-deoxycortisol → Cortisol

DHEA → Androstenedione

CYP17: 17α-hydroxylase

CYP17: C17,20-lyase

Testosterone < 1 ng/dl
Estradiol < 80 pg/dl

< 2 ng/dl
Mechanism of action of abiraterone

- **ACTH** (upregulated by 5-fold)
  - Positive drive
  - **Pregnenolone** → **Deoxycorticosterone** (upregulated by 10-fold)
  - **Corticosterone** (upregulated by 40-fold)
  - **Aldosterone** (downregulated by 1.5-fold)
  - **Suppression of Renin**
  - **Negative feedback**

- **CYP17**: 17α-hydroxylase
  - **17OH-Pregnenolone** → **17OH-Progesterone** (upregulated by 3-fold)
  - **11-deoxycortisol** (upregulated by 4-fold)
  - **Cortisol** (downregulated by 2-fold)

- **DHEA** (upregulated by 3-fold)
  - **Androstenedione** (downregulated by <2 ng/dl)
  - **Testosterone** (downregulated by <1 ng/dl)
  - **Estradiol** (downregulated by <80 pg/dl)

- **Hypokalaemia**
- **Hypertension**
- **Fluid overload**
Phase I/II Study

- Continuous daily dosing
  - 250mg/day to 2000mg/day fasted
- Abiraterone administered without steroids
  - Mineralocorticoid antagonist eplerenone utilized
- No dose limiting toxicity
- Satisfactory dose-proportional pharmacokinetics
- Pharmacodynamic endocrine data
  - Falls in hormone levels below CYP17; increases in hormone levels above CYP17; falls in PSA; CTC
PSA declines with abiraterone acetate: Patients who had failed all hormonal Rx

PSA is a pharmacodynamic endpoint of AR signaling blockade

Resolving bone metastases in patient on abiraterone

- Prior progression on several treatments
- PSA fall from **76 → 5.5** within 3 months
- Circulating tumour cell count fall from 12 to 1
- Resolution of pain
Regression of pelvic nodes

- Prior progression on several hormone treatments
- PSA decline from 34.3 → 0.21 (99%) within 3 months
- Shrinkage of lymph glands shown above on CT scan
Regressing liver disease

Previous 10 m PR on depsipeptide
Duration of response: 12+ months
Post-chemotherapy PSA data (abiraterone administered with prednisolone 10mg/day)

Reid et al, JCO, 2010
CTC counts: Abiraterone trials

• **Chemotherapy naïve study:**
  – 20/54 (37%) ≥5 CTC at baseline
  – 11/20 (55%) decline from >5 to <5 CTC
  – 13/20 (65%) decline by 30%

• **Post-docetaxel study:**
  – 26/34 (76%) ≥5 CTC at baseline
  – 13/26 (50%) decline from >5 to <5 CTC
  – 19/26 (73%) decline by 30%

Taken at baseline and monthly throughout the trial
Relevance of CTC counts

• Our previous studies indicate that:
  – Baseline CTC counts are independently prognostic in multivariate analysis
  – Post-treatment falls in CTC from >5 to <5 significantly associate with overall survival
  – Post-treatment falls in CTC counts >30% significantly associate with overall survival

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

<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>

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

de Bono et al, CCR, 2008
Abiraterone post-chemotherapy Phase III trial

Abiraterone 1000 mg daily
Prednisone 10 mg daily

Placebo daily
Prednisone 10 mg daily

Scher, H and de Bono, J. Cougar Biotechnology
Phase III registration trial for abiraterone

1. **Objective:** Does the addition of abiraterone to prednisone prolong life? Does post-treatment CTC number indicate treatment was effective?

2. **Eligibility:** Progression post 1 or 2 cytotoxic drugs.

3. **Treatment:** Abiraterone plus prednisone vs. Placebo plus prednisone.

4. **Endpoint:** Overall survival.

5. **Conclusion:** Registration. 

*Scher, H and de Bono, J. Cougar Biotechnology*
COU-AA-301 Study Design

Patients
- 1195 patients with progressive, mCRPC
- Failed 1 or 2 chemotherapy regimens, one of which contained docetaxel

Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study (147 sites in 13 countries; USA, Europe, Australia, Canada)

Stratification according to:
- 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 progression with or without PSA progression)

Efficacy endpoints (ITT)

Primary end point:
- OS (25% improvement; HR 0.8)

Secondary end points (ITT):
- TTPP
- rPFS
- PSA response

Abiraterone 1000 mg daily
Prednisone 5 mg BID
N=797

Placebo daily
Prednisone 5 mg BID
n=398

Clinicaltrials.gov identifier: NCT00638690.
COU-AA-301 Statistical Design

Overall Assumption:
- 0.05 two-sided alpha
- 85% Power
- HR=0.80 (Median OS: 12 mo vs. 15 mo)
- One interim analysis and one final analysis planned

<table>
<thead>
<tr>
<th></th>
<th>Planned Interim Analysis</th>
<th>Planned Final Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>534</td>
<td>797</td>
</tr>
<tr>
<td>Cumulative alpha</td>
<td>0.012</td>
<td>0.05</td>
</tr>
</tbody>
</table>

2Q08 3Q08 4Q08 1Q09 2Q09 3Q09 4Q09 1Q10 2Q10 3Q10 4Q10 1Q11

FPI 23
LPI
IDMC
COU-AA-301 Planned Interim Analysis

- **August 20, 2010** – independent data monitoring committee (IDMC) recommended unblinding the study
  - 552 events at time of interim analysis
  - Improvement in overall survival crossed predetermined boundary for stopping
  - IDMC recommended placebo arm patients be offered treatment with abiraterone acetate
## COU-AA-301 Patient Disposition

<table>
<thead>
<tr>
<th></th>
<th>AA (n = 797)</th>
<th>Placebo (n = 398)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects treated</strong></td>
<td>791</td>
<td>394</td>
</tr>
<tr>
<td><strong>Median number of cycles of therapy, range</strong></td>
<td>8 (1-21)</td>
<td>4 (1-21)</td>
</tr>
<tr>
<td><strong>Treatment ongoing</strong></td>
<td>222 (28.1%)</td>
<td>54 (13.7%)</td>
</tr>
<tr>
<td><strong>Treatment discontinued</strong></td>
<td>569 (71.9%)</td>
<td>340 (86.3%)</td>
</tr>
</tbody>
</table>

*Overall median duration of follow up was 12.8 months*
# COU-AA-301 Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>AA (n = 797)</th>
<th>Placebo (n = 398)</th>
<th>Total (n = 1195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>69.0 (42-95)</td>
<td>69.0 (39-90)</td>
<td>69.0 (39-95)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>93.3%</td>
<td>92.7%</td>
<td>93.1%</td>
</tr>
<tr>
<td>Black</td>
<td>3.5%</td>
<td>3.8%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Asian</td>
<td>1.4%</td>
<td>2.3%</td>
<td>1.7%</td>
</tr>
<tr>
<td>ECOG-PS 2</td>
<td>10.7%</td>
<td>11.1%</td>
<td>10.8%</td>
</tr>
<tr>
<td>Significant pain present</td>
<td>44.3%</td>
<td>44.0%</td>
<td>44.2%</td>
</tr>
<tr>
<td>2 Prior chemotherapies</td>
<td>28.2%</td>
<td>28.4%</td>
<td>28.3%</td>
</tr>
<tr>
<td>Radiographic Progression</td>
<td>70.1%</td>
<td>68.6%</td>
<td>69.6%</td>
</tr>
</tbody>
</table>
# COU-AA-301 Baseline Disease Characteristics (1)

## Extent of disease

<table>
<thead>
<tr>
<th></th>
<th>AA (n = 797)</th>
<th>Placebo (n = 398)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone</strong></td>
<td>89.2%</td>
<td>90.4%</td>
</tr>
<tr>
<td><strong>Node</strong></td>
<td>45.4%</td>
<td>41.5%</td>
</tr>
<tr>
<td><strong>Visceral Metastasis</strong></td>
<td>29.0%</td>
<td>24.1%</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>11.3%</td>
<td>7.6%</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td>13.0%</td>
<td>11.4%</td>
</tr>
<tr>
<td><strong>Other Visceral</strong></td>
<td>5.8%</td>
<td>5.3%</td>
</tr>
</tbody>
</table>
## COU-AA-301 Baseline Disease Characteristics (2)

<table>
<thead>
<tr>
<th></th>
<th>AA (n = 797)</th>
<th>Placebo (n = 398)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSA (median, ng/mL)</strong></td>
<td>128.8</td>
<td>137.7</td>
</tr>
<tr>
<td><strong>Hemoglobin (median, g/dL)</strong></td>
<td>11.8</td>
<td>11.8</td>
</tr>
<tr>
<td><strong>Alkaline Phosphatase (median, IU/L)</strong></td>
<td>133.5</td>
<td>134.0</td>
</tr>
<tr>
<td><strong>LDH (median, IU/L)</strong></td>
<td>223.0</td>
<td>237.5</td>
</tr>
</tbody>
</table>
COU-AA-301: Abiraterone Acetate Improves Overall Survival in mCRPC

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
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 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>

BPI; Brief Pain Inventory, ALK-P, alkaline phosphatase
COU-AA-301: All Secondary End Points Achieved Statistical Significance

<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>
## COU-AA-301: Summary of AEs

<table>
<thead>
<tr>
<th></th>
<th>AA (n = 791)</th>
<th></th>
<th>Placebo (n = 394)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grades 3/4</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>
<td>99.0%</td>
<td>58.4%</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>37.5%</td>
<td>32.1%</td>
<td>41.4%</td>
<td>35.3%</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>18.7%</td>
<td>10.5%</td>
<td>22.8%</td>
<td>13.5%</td>
</tr>
<tr>
<td>AEs leading to death</td>
<td>11.6%</td>
<td></td>
<td>14.7%</td>
<td></td>
</tr>
<tr>
<td>Deaths within 30 days of last dose</td>
<td>10.5%</td>
<td></td>
<td>13.2%</td>
<td></td>
</tr>
<tr>
<td>Underlying disease</td>
<td>7.5%</td>
<td></td>
<td>9.9%</td>
<td></td>
</tr>
<tr>
<td>Other specified cause</td>
<td>2.9%</td>
<td></td>
<td>3.3%</td>
<td></td>
</tr>
</tbody>
</table>
COU-AA-301: AEs 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>Fluid retention</td>
<td>30.5%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>17.1%</td>
<td>3.8%</td>
</tr>
<tr>
<td>LFT abnormalities</td>
<td>10.4%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9.7%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>13.3%</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

LFT, liver function test
2010 has been a very good year for CRPC: OS Benefit in Recent CRPC Trials

<table>
<thead>
<tr>
<th>Trial/Agent Approved</th>
<th>Disease state</th>
<th>Comparator</th>
<th>Hazard Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPACT (Provenge vaccine) 2010 (Kantoff et al)</td>
<td>Chemo-näive CRPC</td>
<td>Placebo</td>
<td>0.775</td>
<td>0.032</td>
</tr>
<tr>
<td>TAX327 (Docetaxel) 2004 (Tannock et al)</td>
<td>Chemo-näive CRPC</td>
<td>Mitoxantrone Prednisone</td>
<td>0.76</td>
<td>0.009</td>
</tr>
<tr>
<td>TROPIC (Cabazitaxel) 2010 (de Bono et al)</td>
<td>Post-Docetaxel CRPC</td>
<td>Mitoxantrone Prednisone</td>
<td>0.70</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COU-AA-301 (Abiraterone acetate) 2010 (de Bono et al)</td>
<td>Post-Docetaxel CRPC</td>
<td>Placebo Prednisone</td>
<td>0.646</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Conclusion

• **Advanced prostate cancer** is neither hormone refractory nor androgen independent and remains nuclear steroid receptor driven
  – Role of ERα remains to be defined
• Multiple lines of treatment for advanced prostate cancer
  – Optimal sequence of administration needs defined
• **Hypothesis 2011**: At progression on these new agents, advanced prostate cancer remains driven by nuclear steroid receptors.