Endocrine manipulations for castration-resistant prostate cancer

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The Institute of Cancer Research and the Royal Marsden NHS Foundation Trust
• Employee of the Institute of Cancer Research (ICR) that has a commercial interest in abiraterone. I’m on The ICR rewards to inventors list of abiraterone.

• Investigator for trials sponsored by Janssen, Medivation/Astellas, Arno.

• Received:-
  – Consulting fees and travel support from Janssen-Cilag, Veridex, Roche/Ventana, Astellas, Medivation, Novartis, Millennium Pharmaceuticals, Dendreon and Abbott Laboratories.
  – Speaker’s fees from Janssen, Ipsen, Takeda and Sanofi-Aventis.
  – Grant support from Janssen, AstraZeneca, Arno
The definition of CRPC requires a rising PSA following castration in the presence of:

1. Confirmed testosterone levels <50ng/dl (<1.7 nmol/l)
2. Prior treatment with bicalutamide or another “vintage” anti-androgen
3. Both
4. Neither
The changing face of CRPC treatment

**Castrate Sensitive**

- Local therapy
- LHRHa

- Rad223
- COU-302
- PREVAIL
- Abiraterone prednisolone/Enzalutamide*

**Castration-Resistant Disease**

- Rad223
- ALSYMPCA
- TAX327, SWOG99-16
- Docetaxel
- COU-301
- AFFIRM
- Abiraterone Prednisolone/Enzalutamide*
- TROPIC
- Cabazitaxel

- Retrospective data suggest very limited activity

* Alphabetical order and does not denote sequencing preference
The changing face of CRPC treatment

Tumour Volume and Activity

Local therapy

LHRHa

Castrate Sensitive

Castration-Resistant Disease

Time

* Alphabetical order and does not denote sequencing preference
• Whistle-stop tour of regulatory Phase III trials

• Mechanisms of action of abiraterone and enzalutamide (including some often forgotten details)

• Making clinical decisions in the absence of evidence (with audience participation)
Abiraterone post-docetaxel

Median OS Benefit: 4.6 Months

HR (95% CI): 0.74 (0.64-0.86)
p < 0.0001

AA median OS (95% CI):
15.8 months (14.8-17.0)

Placebo median OS (95% CI):
11.2 months (10.4-13.1)

- Median duration of follow-up: 20.2 months
- Median duration of treatment: AA, 8 months vs placebo, 4 months

de Bono et al, NEJM 2011
Enzalutamide post-docetaxel

**Survival (%)**

- MDV3100: 18.3 months (95% CI: 17.3, NYR)
- Placebo: 13.6 months (95% CI: 11.3, 15.8)

**HR = 0.631 (0.529, 0.752) P < 0.0001**

37% Reduction in Risk of Death

**Median OS Benefit: 4.8 Months**

Scher H et al, NEJM 2012
Enzalutamide pre-chemotherapy

Enzalutamide vs Placebo

Radiographic Progression-Free Survival (%)

Hazard ratio, 0.19 (95% CI, 0.15–0.23)
P<0.001

Overall Survival (%)

Hazard ratio, 0.71 (95% CI, 0.60–0.84)
P<0.001

<table>
<thead>
<tr>
<th>Use of prior antiandrogen therapies – no. (%)</th>
<th>760 (87.2)</th>
<th>730 (86.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of prior antiandrogen therapies – no. (%)</td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>112 (12.8)</td>
<td>115 (13.6)</td>
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<tr>
<td>1</td>
<td>573 (65.7)</td>
<td>561 (66.4)</td>
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<tr>
<td>2</td>
<td>165 (18.9)</td>
<td>151 (17.9)</td>
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<tr>
<td>≥3</td>
<td>22 (2.5)</td>
<td>18 (2.1)</td>
</tr>
</tbody>
</table>

Beer et al, NEJM 2014
Abiraterone pre-chemotherapy

ITT Population (n = 1088)

HR (95% CI): 0.52 (0.45, 0.61)
p < 0.0001

Progression-free Survival (%)

Time to Progression or Death (Months)

Survival (%)

Time to Death (Months)

Abiraterone (median, mos): NR
Prednisone (median, mos): 27.2
HR (95% CI): 0.75 (0.61-0.93)
P value: 0.0097

Ryan et al. NEJM 2013
Abiraterone and OS in chemo-naïve CRPC

HR (95% CI): 0.81 (0.70-0.93)

p Value: 0.0033

Overall Survival (%)

Time to Death (Months)

Abiraterone, 34.7 mos
Prednisone, 30.3 mos

Median follow-up of 49.2 mos

Abiraterone treatment effect more pronounced when adjusting for 44% of prednisone patients who received subsequent abiraterone (HR = 0.74)

26-30 September 2014, Madrid, Spain
Updated COU-302 survival analysis

Required p Value for Significance

- IA1 < 0.0001
- IA2 0.0008
- IA3 0.0035
- FA 0.0384

Actual p Value Observed

- 2009: IA1 0.6926
- 2010: 0.75 (0.61-0.93)
- 2011: 0.79 (0.66-0.95)
- 2012: 0.79 (0.66-0.95)
- 2013: 0.81 (0.70-0.93)
- 2014: FA 0.0033
- 2015: FA 0.0033

Ryan CJ et al
COU-302 and PREVAIL support early versus later use of abi/enza

<table>
<thead>
<tr>
<th></th>
<th>Abiraterone n (%)</th>
<th>Prednisone n (%)</th>
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<tbody>
<tr>
<td>No. with selected subsequent therapy for mCRPC</td>
<td>365 (67)</td>
<td>435 (80)</td>
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<tr>
<td>Abiraterone</td>
<td>69 (13)</td>
<td>238 (44)</td>
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<td>Cabazitaxel</td>
<td>100 (18)</td>
<td>105 (19)</td>
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<td>Docetaxel</td>
<td>311 (57)</td>
<td>331 (61)</td>
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<td>Enzalutamide</td>
<td>87 (16)</td>
<td>54 (10)</td>
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<td>Ketoconazole</td>
<td>42 (8)</td>
<td>68 (13)</td>
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<td>Radium-223</td>
<td>20 (4)</td>
<td>7 (1)</td>
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<td>Sipuleucel-T</td>
<td>45 (8)</td>
<td>32 (6)</td>
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</tbody>
</table>

*Includes 93 patients who received abiraterone per protocol amendments.*
Mechanism of action of abiraterone

Attard et al, J Clin Oncol 2008
Exogenous glucocorticoids suppress upstream steroids

Although mineralocorticoid excess manifests in up to 30% of patients with prednisone 5mg bid
Reversal of resistance by addition of dexamethasone to single-agent abiraterone

Attard et al, J Clin Oncol 2008
Reversal of resistance

Attard et al J Clin Oncol 2009
Why use 1000mg abiraterone?

Attard et al, J Clin Oncol 2008
With food or without?

Attard et al. JCO 2008

Ryan et al. JCO 2010

Journal of Clinical Oncology

Flushing Oral Oncology Drugs Down the Toilet

Mark J. Ratain, The University of Chicago, Chicago, IL
Abiraterone with LHRHa vs abiraterone alone

O'Donnell et al, Br J Cancer 2004
Abiraterone inhibits cell growth stimulated by R1881

- AR antagonism in addition to inhibition of steroidogenesis?
Abiraterone binds and inhibits the AR

Richards et al Cancer Res 2012
Avoid spironolactone but beware of eplerenone

Richards et al, Cancer Res 2012
Upregulation of AR alone sufficient to cause CRPC

Chen et al, Nature Med, 2004
Enzalutamide: Second Generation Antiandrogen

Tran et al. Science 2009; 324: 787-790
Enzalutamide: Second Generation Antiandrogen

Tran et al. Science 2009; 324: 787-790
AR F876L mutation
Dose selection of enzalutamide

Scher et al, The Lancet, 2010

Increasing fatigue requiring dose reduction

Rare witnessed seizures

Scher et al, The Lancet, 2010
Increased hormone levels reduce inhibition of AR activity by MDV3100

Richards et al, Cancer Res 2012
• Enzalutamide or abiraterone should now be initiated prior to bicalutamide or other vintage anti-androgens for the majority of patients

1. Yes
2. No
• **Hypothesis**: Delay to initiation of most effective treatments in progressing patients is detrimental

• TERRAIN trial
• 375 patients enza vs bicalutamide
• Significant increase in PFS (HR = 0.44; 95% CI, 0.34-0.57; p < 0.0001).
• Median PFS was 15.7 months for enza vs 5.8 months for bicalutamide
- Bulky, rapidly progressing metastases
  • GIVEN THE POOR METHODS FOR PREDICTING RESPONSE, THE MORE EFFECTIVE TREATMENT SHOULD BE INITIATED IMMEDIATELY TO DELAY SYMPTOMS AND ALLOW SUBSEQUENT USE OF ALL LIFE-PROLONGING TREATMENTS BEFORE FITNESS LEVELS DETERIORATE

- Asymptomatic with rising PSA but low volume metastases
  • Bicalutamide is at least as well tolerated but significantly cheaper – why not try bicalutamide 1st?
Castration-resistant state – hypothetical scenarios

FACT: \( b > a \)

???: \( c \gg a+b \)
Castration-resistant state – hypothetical scenarios

FACT: $b > a$

???: $c >> a + b$

SCENARIO 1
OMIT VINTAGE AA

SCENARIO 2
USE VINTAGE AA
• The results of the COU-302 and PREVAIL trials can be extrapolated to symptomatic chemotherapy-naïve patients

• Yes
• No
• Single-agent steroids should be initiated before abiraterone or enzalutamide

• Yes

• No
PSA declines with single-agent steroids
Abiraterone or enzalutamide is the treatment of choice for a symptomatic patient who has progressed on the alternative novel AR targeting agent.

- Yes
- No
<table>
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<tr>
<th>Cohort size</th>
<th>Prior treatment</th>
<th>PSA response</th>
<th>RX response</th>
<th>Survival</th>
<th>Comments</th>
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<td>30% PSA decline</td>
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<td>Partial response</td>
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<td>6.2–8.1*</td>
<td>Not reported</td>
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<td>Median OS not reached</td>
<td>Median OS not reached</td>
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<td>2.8 m (95% CI: 2–3.6)</td>
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<td>6.6–NR</td>
<td>2.6–3.7</td>
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CI=confidence interval; m=months; NR=not recorded; OS=overall survival; PFS=progression-free survival; PSA=prostate-specific antigen; Rx=radiographic.

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<td></td>
<td>Anti-androgens: 100%</td>
<td>30% PSA decline: 13/35 (37%)</td>
<td>Partial response: 4/24 (16.7%)</td>
<td>Overall survival: 12.5 m (95% CI: 10.6–19.4)</td>
<td>None of the abiraterone-refractory patients responded to docetaxel</td>
</tr>
<tr>
<td>Mezynski et al.</td>
<td>Anti-androgens: 100%</td>
<td>30% PSA decline: 14/23 (60.8%)</td>
<td>Partial response: 3/20 (15%)</td>
<td>Overall survival: 20.3 m (95% CI: 14–26.6)</td>
<td>Results comparable to TROPIC - Inferior activity in control group of abiraterone/enzalutamide naïve patients - Higher rates of 50% PSA decline in patients with no previous PSA response to abiraterone</td>
</tr>
<tr>
<td>Schweizer et al.</td>
<td>Anti-androgens: 92%</td>
<td>30% PSA decline: 13/24 (54.2%)</td>
<td>Overall survival: NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Aggarwal et al.</td>
<td>Anti-androgens: 4%**</td>
<td>30% PSA decline: 15/23 (65%)</td>
<td>Overall survival: 12.4 m (95% CI: 8.2–19.6)</td>
<td>- Similar rate of response in patients with primary and acquired resistance to abiraterone</td>
<td></td>
</tr>
<tr>
<td>Azad et al.</td>
<td>Docetaxel: 57%</td>
<td>50% PSA decline: 37/49 (76%)</td>
<td>Overall survival: NR</td>
<td>11.7 m (95% CI: 3.1–5)</td>
<td>No association between response to abiraterone and response to docetaxel</td>
</tr>
<tr>
<td>Pezaro et al.</td>
<td>Abiraterone: 100%</td>
<td>30% PSA decline: 21/37 (56.8%)</td>
<td>Partial response: 3/20 (15%)</td>
<td>Overall survival: 20.3 m (95% CI: 14–26.6)</td>
<td>Compared sequence cabazitaxel → abiraterone vs. abiraterone → cabazitaxel</td>
</tr>
<tr>
<td>Sella et al.</td>
<td>Abiraterone: 100%</td>
<td>50% PSA decline: 6/19 (31.5%)</td>
<td>Partial response: 2/13 (15.3%)</td>
<td>Overall survival: 8.2 m (95% CI: 3.3–13.1)</td>
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<tr>
<td>Wissing et al.</td>
<td>Abiraterone: 100%</td>
<td>50% PSA decline: 18/69 (26.5%)</td>
<td>PFS: 3.2 m (95% CI: 2.5–3.8)</td>
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<tr>
<td>Al Nakouzi et al.</td>
<td>Abiraterone: 100%</td>
<td>30% PSA decline: 48/79 (62%)</td>
<td>Overall survival: 10.9 m (95% CI: 8–14)</td>
<td>No preclinical evidence of cross-resistance</td>
<td></td>
</tr>
</tbody>
</table>

CI=confidence interval; m=months; NR=not recorded; PFS=progression-free survival; PSA=prostate-specific antigen; Rx=radiographic.