

## Novel Hormone Therapies for PCa

Hein Van Poppel

## Disclosures

Advisory Board member, Expert, Consultant or Investigator for the following companies:

1. ABBOTT
2. AMGEN
3. ASTELLAS
4. ASTRAZENECA
5. COUGAR, JANSSEN-CILAG
6. FERRING
7. IPSEN

## New patients – new options?

- 58 years old, active lifestyle
- PSA 8 ng/ml, 2 +ve Biopsies Gleason 7

## HoT in PCa

- 1939: **Orchiectomy**
- 1941: **Oestrogens**
- 1985: **LHRH-Agonists**  
**Anti-androgens**
- 1989: **MAB**
- 2000: **GnRH-Antagonists**
- 2003: **Anti-androgen Monotherapy**
- 2008: **Abiraterone**  
**MDV 3100**


## LHRH agonist = Standard in patients requiring hormone therapy

## Androgen deprivation therapy (ADT) with LHRHa-aa

Agonist	Brand Name	Formulation
Histrelin	Vantas <sup>02</sup>	1-year implant
Leuprolide	Eligard <sup>03</sup>	1-, 3-, 4- or 6-month injection
	Lupron Depot <sup>04</sup>	1-, 3-, 4- or 6-month injection
Goserelin	Zoladex <sup>05</sup>	3-month injection
Triptorelin	Trelstar <sup>06</sup> LA <sup>6</sup> + Trelstar <sup>06</sup> Depot <sup>7</sup>	1-month (depot) or 3-month (LA) injection
	Antagonist	Brand Name
Degarelix	Firmagon <sup>08</sup>	1-month injection

## How to reduce side-effects and improve quality of life of patients receiving hormone therapy

**LHRH is the standard**




Use intermittent administration of LHRH agonists

IAD

## How to reduce side-effects and improve quality of life of patients receiving hormone therapy

**LHRH is the standard**



Use antiandrogen monotherapy to avoid castration-effect

Bicalutamide 150

## Management of HRPC Hormone Resistant PCa

i.e. LHRH or MAB Resistance

- Role of secondary hormonal manipulations - AA withdrawal, second line
- Chemotherapy: Taxotere –Cabazitaxel
- More potent anti-androgens?
- Intracellular androgen production blockade?

## Second-line hormonal manipulations

### 1. Anti-androgen withdrawal syndrome

Total	Drug	Patients (n)	% of patients with 50% PSA response	Duration (months)
Scher et al	Flut	57	28	4
Small et al	Flut	82	15	3.5
Figg et al	Flut	21	33	3.7
Herrada et al	Flut	39	28	3.3
Schellhammer et al	Flut	8	50	NR
	Bical	14	29	NR
Nieh	Bical	3	33	6
<b>Total</b>		<b>224</b>	<b>25</b>	<b>?</b>

## Second-line hormonal manipulations

### 2. Other hormonal treatments

- Change LHRHa-aa, another anti-androgen
- Adrenal androgen inhibitor (Ketoconazole)
- Estrogens, Estramustine phosphate
- Corticosteroids
  - ↳ Very few / no RCT
  - ↳ No proven efficacy on survival
  - ↳ Only PSA response
    - ± 20-40 %
    - 2-6 months

## And after second-line hormonal manipulations ?

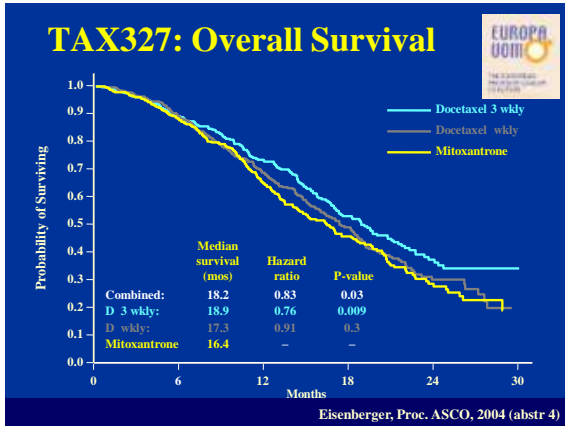
### Taxotere 3-weekly

Tax 327	Docetaxel Q3W (n=335)	Docetaxel Weekly (n=334)	Mitoxantrone (n=337)
3-yr survival rate*	17.2% (12.8-23.0)	16.4% (12.1-22.4)	12.8% (9.1-17.8)
p-value	0.005	0.14	

\*95% confidence Interval indicated

Docetaxel has created an unmet medical need in the 2nd-line setting

D. R. Berthold et al, 2007 ASCO Prostate Cancer Symposium, Abstract 147



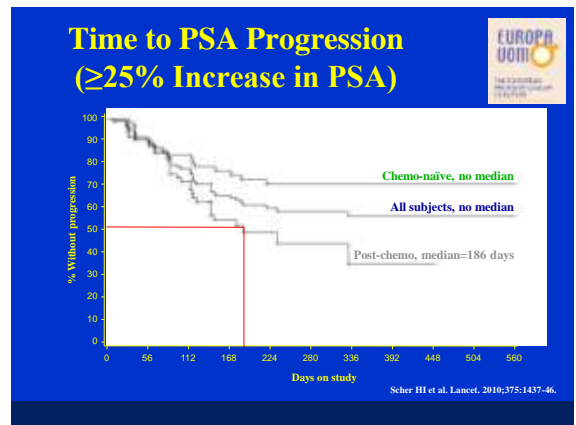
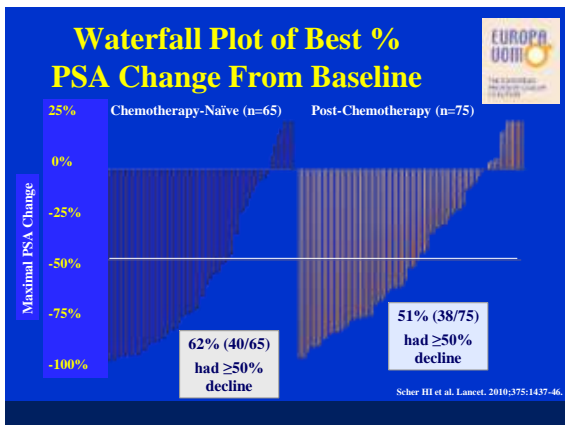
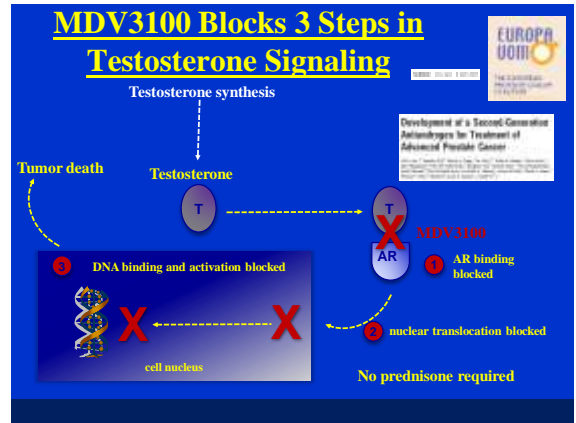
### Management of HRPC Hormone Resistant PCA

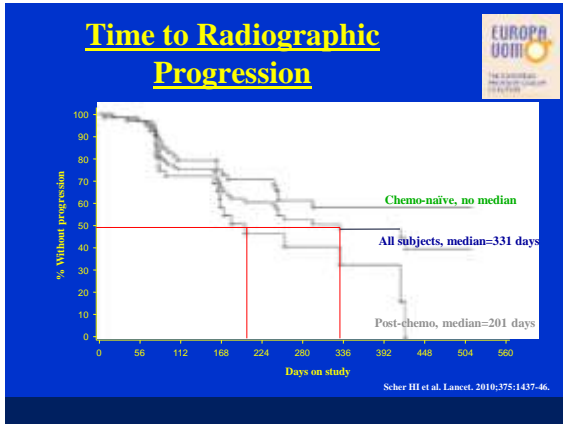
i.e. LHRH or MAB Resistance

- Role of secondary hormonal manipulations  
- AA withdrawal, second line
- Chemotherapy: Taxotere –Cabazitaxel
- More potent anti-androgens?
- Intracellular androgen production blockade?

### MDV3100 : Medivation

- Is an oral Androgen Receptor(AR)-antagonist
- Binds to AR with a 5-8x greater affinity than bicalutamide
- Triple-acting mode
  - impedes translocation of AR to nucleus of cell and inhibits AR-DNA binding
  - impairs coactivator recruitment
  - induces apoptosis
- Works strictly as an antagonist





### MDV3100 Tolerability

	Dosage, mg/day		Total (n = 140)
	≤240 (n = 87)	>240 (n = 53)	
<b>Grade 3-4* adverse events occurring in &gt;2 patients</b>			
Fatigue	5 (6%)	11 (21%)	16 (11%)
Anemia	3 (3%)	1 (2%)	4 (3%)
Arthralgia	2 (2%)	1 (2%)	3 (2%)
Asthenia	-	3 (6%)	3 (2%)
Seizure	-	3 (6%)	3 (2%)
<b>Adverse events leading to discontinuation</b>			
Seizure	-	3 (6%)	3 (2%)
Rash	-	2 (4%)	2 (1%)
Nausea/Vomiting	-	1 (2%)	1 (1%)
Fatigue	1 (2%)	-	1 (1%)
MI	-	1 (2%)	1 (1%)

- Well tolerated
- Maximum tolerated dose (MTD): 240 mg/d
- Two witnessed seizures (360 and 600 mg/day) and 1 possible un witnessed seizure (480 mg/day)
- Both patients with witnessed seizures were on concomitant seizure-associated medications

Scher HI et al. Lancet. 2010;375:1437-46.

- ### MDV3100 Medivation
- phase I/II trial with 140 CRPC-patients (Lancet 2010;375:1437-46)
    - ≥50% decline in PSA in 78 of 140 (56%)
    - soft-tissue response in 13 of 59 (22%)
    - stabilized bone disease in 61 of 109 (56%)
    - conversion to favorable circulating tumor-cell counts in 25 of 51 (49%)
    - median time to radiological progression 47 weeks (upper limit 95% CI not reached)
  - phase III trials (AFFIRM) running with CRPC-patients previously treated with docetaxel

- ### Management of HRPC Hormone Resistant PCa
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### Prostate cancer is androgen-driven

- Androgens produced at all 3 sources stimulate tumor proliferation
- Androgen deprivation therapies primarily target testicular androgens

Danila DC et al. J Clin Oncol. 2010;28(9):1496-1501.

### ADT fails to maintain low intracellular testosterone

“...We conclude that intracrine steroidogenesis may permit tumors to circumvent low levels of circulating androgens. Maximal therapeutic efficacy in the treatment of castration-resistant prostate cancer will require novel agents capable of inhibiting intracrine steroidogenic pathways within the prostate tumor microenvironment.”

Montgomery RB, Cancer Res 2008;68:4447-54

## Why develop another CRPC hormonal agent ?

LHRH analogues do not inhibit adrenal androgen synthesis

Responses observed with ketoconazole, but poor tolerability

Residual androgens persist in CRPC tissues despite LHRHa therapy

- Intracrine or paracrine signaling

CRPC remains driven by a ligand-activated androgen receptor (AR)

- AR overexpression, TMPRSS2-ERG

Antandrogen

## ADT fails to maintain low intracellular testosterone

Maintenance of intratumoral androgens in M+ PCa: a mechanism for castration-resistant tumor growth

Group	T (ng/g)	DHT (ng/g)
BPH	~2.0	~0.1
PCa Primary	~2.8	~0.1
Control	~0.1	~0.1
M+ CRPCa	~1.0	~0.1

Adapted from Montgomery RB, Cancer Res 2008; 68:4447-54

## ADT fails to maintain low intracellular T

Adapted from Montgomery RB, Cancer Res 2008;68:4447-54

## Decrease intracellular testosterone synthesis?

Abiraterone acetate is a selective inhibitor of CYP17A1

Adapted from Montgomery RB, Cancer Res 2008;68:4447-54

## Abiraterone Acetate


- CYP17 is key to androgenic steroid synthesis
- Oral, selective inhibitor of CYP17 – one enzyme, dual function
  - 17 $\alpha$ -hydroxylase
  - C<sub>17,20</sub>-lyase
- Inhibits testosterone production in testis, adrenal glands and prostate

MW = 391.55

3 $\beta$ -Acetoxy-17 $\beta$ -(3-pyridyl)androst-5,16-diene

## Abiraterone: Multiple inhibition of androgen synthesis

## COU-AA-301: Trial Design




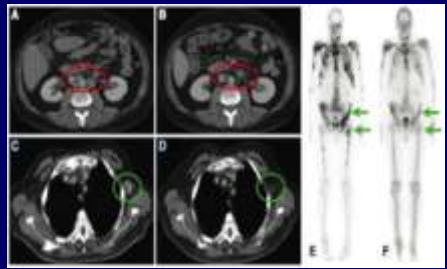
**Patients With Post-Docetaxel CRPC**  
175 sites in NA, Europe and Australia

**Placebo + Prednisone**  
Placebo 1000 mg PO daily; prednisone 5 mg bid

**Abiraterone Acetate + Prednisone**  
Abiraterone 1000 mg PO daily; prednisone 5 mg bid


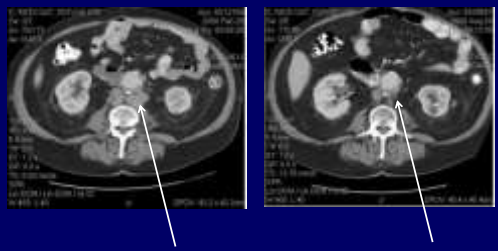
Study Chairs:  
Dr. Howard Scher  
Dr. Johann De Bono

## Measurable Disease Responses


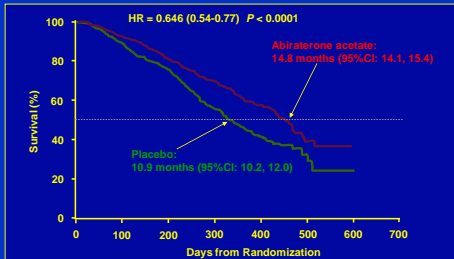



Reid AHM et al. J Clin Oncol. 2010;28:1489-1495

## Objective Response





## COU-AA-301: Overall Survival

de Bono et al. ESMO abstract LBA5, 2010  
Slide adapted of J. de Bono


## COU-AA-301: Secondary End Points



	AA (n = 797)	Placebo (n = 398)	HR 95% CI	P Value
TTPP (months)	10.2	6.6	0.58 (0.46, 0.73)	< 0.0001
rPFS (months)	5.6	3.6	0.67 (0.59, 0.78)	< 0.0001
PSA response rate				
Total	38.0%	10.1%		< 0.0001
Confirmed	29.1%	5.5%		< 0.0001

de Bono et al. ESMO abstract LBA5, 2010  
Slide adapted of J. de Bono

## COU-AA-301: AEs of Special Interest



	AA (n = 791)		Placebo (n = 394)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Fluid retention	30.5%	2.3%	22.3%	1.0%
Hypokalaemia	17.1%	3.8%	8.4%	0.8%
LFT abnormalities <small>(Liver function tests)</small>	10.4%	3.5%	8.1%	3.0%
Hypertension	9.7%	1.3%	7.9%	0.3%
Cardiac disorders	13.3%	4.1%	10.4%	2.3%

de Bono et al. ESMO abstract LBA5, 2010  
Slide adapted of J. de Bono

## COU-AA-301 Conclusions

- AA plus prednisone significantly improves OS and rPFS in patients who progressed after docetaxel
  - Median OS 14.8 vs 10.9 months with placebo
  - Median time to PSA progression and to rPFS significantly improved
- AA generally well tolerated
  - AEs more common with AA included:
    - Fluid retention
    - Hypokalaemia
    - LFT abnormalities
    - Hypertension

de Bono et al, ESMO abstract LBA5, 2010  
Slide adapted of J. de Bono

## OS Benefit in Recent CRPC Trials

Trial/ Agent Approved	Disease state	Comparator	Hazard Ratio	P value
IMPACT (Provenge vaccine) 2010	Chemo-naïve CRPC	Placebo	0.775	0.032
TAX327 (Docetaxel) 2004	Chemo-naïve CRPC	Mitoxantrone Prednisone	0.76	0.009
TROPIC (Cabazitaxel) 2010	Post-Docetaxel CRPC	Mitoxantrone Prednisone	0.70	<0.0001
COU-AA-301 (Abiraterone acetate) 2010	Post-Docetaxel CRPC	Placebo Prednisone	0.646	<0.0001

de Bono et al, ESMO abstract LBA5, 2010  
Slide adapted of J. de Bono

## COU-AA-302: Phase III Initiated April 2009

- Study ongoing, enrollment complete, results awaited for 2011-2012

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1:1

Abiraterone acetate 1000 mg/day,  
(4 x 250-mg tablets PO,  
5 mg prednisone BID)

Placebo + 5 mg prednisone BID

N=1088

- Primary endpoints: OS and rPFS
- Eligibility criteria: Asymptomatic or mildly symptomatic metastatic CRPCa

Abbreviation: rPFS=radiographic progression-free survival  
Data on file, Centocor Ortho Biotech Inc.

## TAKE HOME MESSAGE

Established use of hormonal therapy

- LHRH-a and LHRH-aa

Worth considering

- Pure anti-androgen or Intermittent Deprivation

New hope

- Medivation and Abiraterone

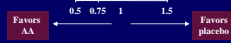
## Backup

## CRPC New agents/new challenges

Pre-docetaxel	Docetaxel	Post-docetaxel
<ul style="list-style-type: none"> <li>Sipuleucel-T</li> <li>PROSTVAC</li> <li>ZD4054</li> <li>Abiraterone</li> </ul>	<ul style="list-style-type: none"> <li>Dasatinib</li> <li>Atrasentan</li> <li>ZD4054</li> <li>Aflibercept</li> <li>Bevacizumab</li> <li>Lenalidomide</li> </ul>	<ul style="list-style-type: none"> <li>Cabazitaxel</li> <li>Abiraterone</li> <li>MDV3100</li> <li>Sunitinib</li> </ul>

### Survival over patient sub-groups

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



de Bono et al. ESMO abstract LBAS, 2010  
 Slide adapted of J. de Bono

BPI: Brief Pain Inventory, ALK-P, alkaline phosphatase