

# **Case #7: Castration-Resistant Prostate Cancer: Optimal Management of a Patient with Good Performance Status**

**Camillo Porta, MD**

**Medical Oncology**

**IRCCS San Matteo University Hospital Foundation**

**Pavia, Italy**

# Case Report

- **67-year-old man with a 10-year history of hypertension well controlled on medication**
- **4 years ago—diagnosis of prostate cancer (Gleason score: 7 [4 + 3]) with bone metastases**
- **Initially treated with luteinizing hormone–releasing hormone (LHRH) agonist every 3 months with prostate-specific antigen (PSA) normalization**
- **2 months ago—PSA increase to 22 ng/mL, with progressive disease (PD) on bone scan**
- **No response after addition of flutamide, nor after flutamide withdrawal**
- **Presently, performance score (PS) = 1 (fatigue, bone pain); bone lesions at pelvis and spine; enlarged lymph nodes along aorta and vena cava**

# Options to Consider

- **Changing antiandrogen to high-dose bicalutamide 150-250 mg daily**
- **Ketoconazole**
- **Clinical trial of abiraterone acetate (abiraterone + prednisone/prednisolone vs placebo + prednsione/prednisolone)**
- **Sipuleucel-T vaccine**
- **Chemotherapy with docetaxel**

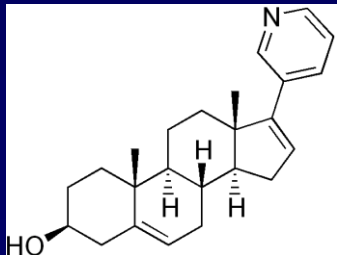
# My Choice

- **Changing antiandrogen to high-dose bicalutamide 150-250 mg daily**
- **Ketoconazole**
- **Clinical trial of abiraterone acetate (abiraterone + prednisone/prednisolone vs placebo + prednsione/prednisolone)**
- **Sipuleucel-T vaccine**
- **Chemotherapy with docetaxel**

# Peculiarities of Castration-Resistant Prostate Cancer to Consider

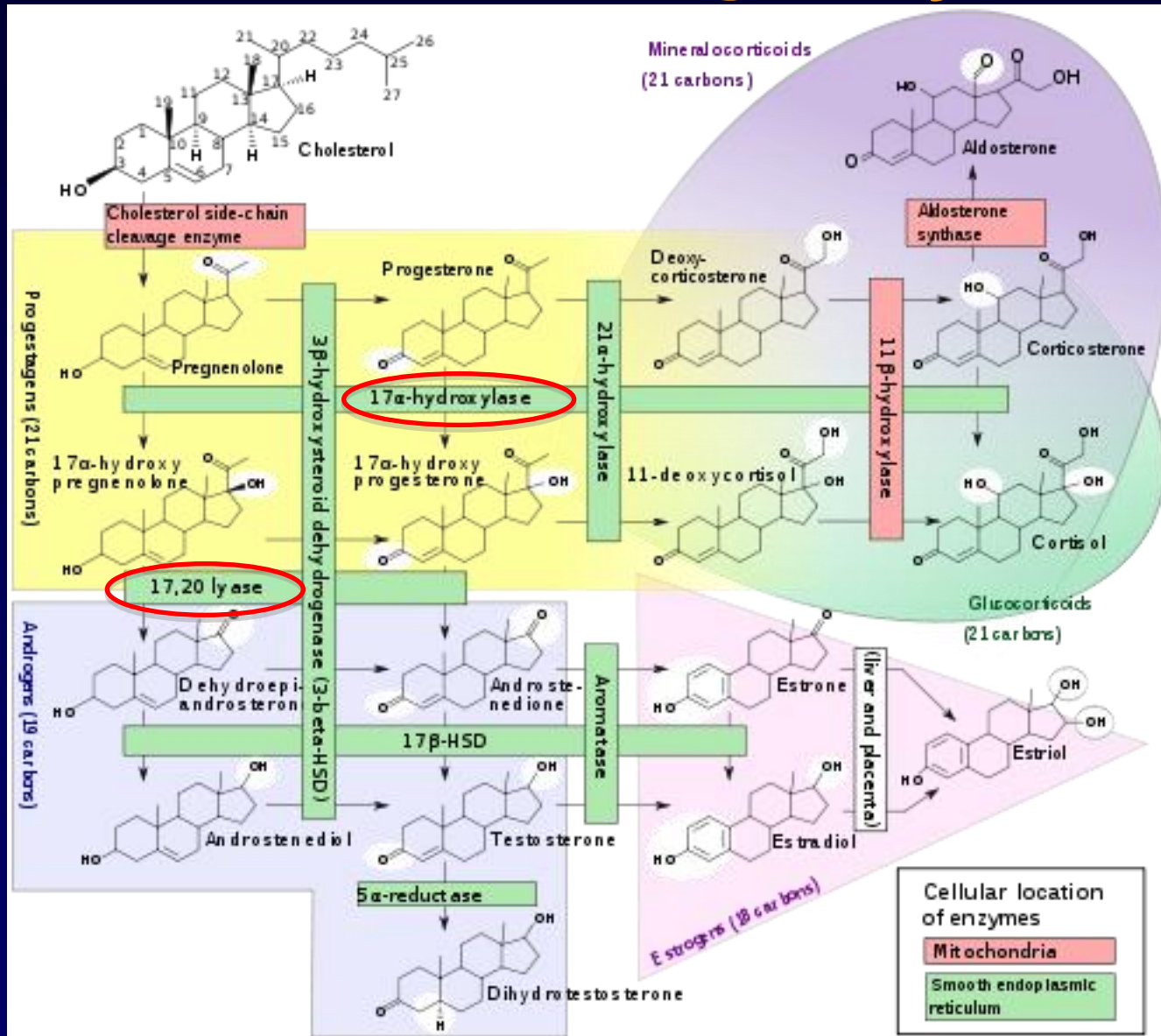
Evidence is accumulating that castration-resistant prostate cancer frequently remains hormone driven, by using adrenal hormones or through intracrine synthesis

CYP17A1 (or 17- $\alpha$ -hydroxylase or 17,20-lyase) is a cytochrome P450 enzyme responsible for androgen and estrogen synthesis from adrenal hormones through progestagens



Abiraterone is a potent, selective, and irreversible inhibitor of CYP17A1

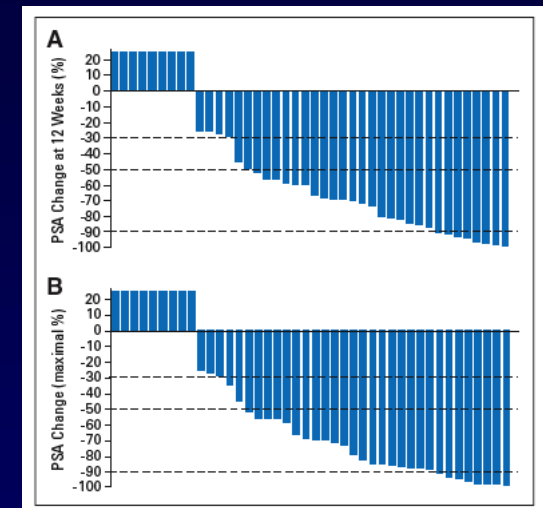
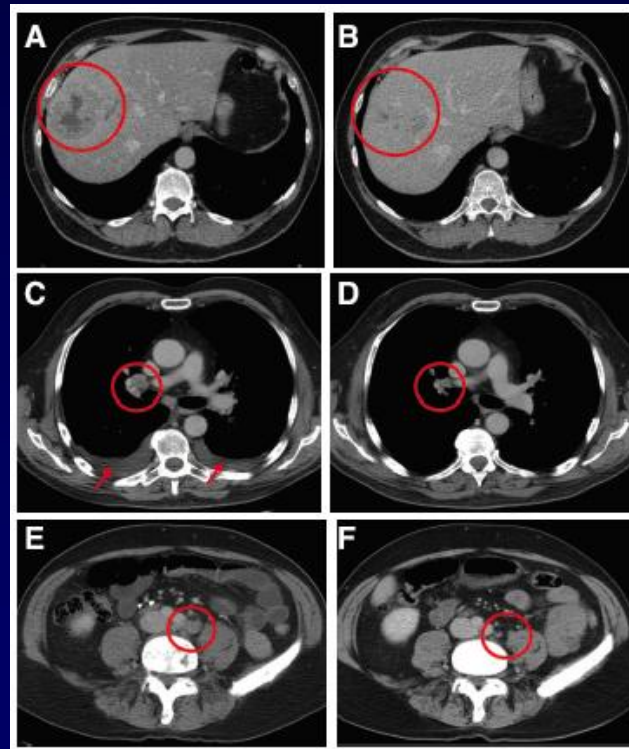
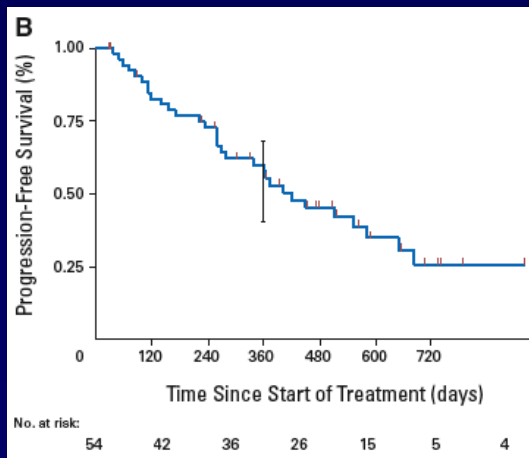
# CYP17A1 and Androgen Synthesis



# Why Abiraterone?

In a phase I-II trial in castration-resistant prostate cancer patients, abiraterone proved able to:

- Reduce PSA
- Shrink tumor
- Induce a long time to PSA increase



# Another Credible Option

- **Changing antiandrogen to high-dose bicalutamide 150-250 mg daily**
- **Ketoconazole**
- **Clinical trial of abiraterone acetate (abiraterone + prednisone/prednisolone vs placebo + prednsione/prednisolone)**
- **Sipuleucel-T vaccine**
- **Chemotherapy with docetaxel**

# Another Credible Option

In 2004, docetaxel (+ prednisone) proved to be superior to the old standard of treatment (ie, mitoxantrone and prednsione), thus becoming the new standard of care for hormone-refractory prostate cancer (HRPC)

## TAX 327: Study Design

### Stratification:

Pain level  
PPI  $\geq 2$  or AS  $\geq 10$   
vs  
PPI  $< 2$  or AS  $< 10$

KPS  
 $\leq 70$  vs  $\geq 80$

R  
A  
N  
D  
O  
M  
I  
Z  
E

Docetaxel 75 mg/m<sup>2</sup> q 3 wk +  
Prednisone 5 mg bid

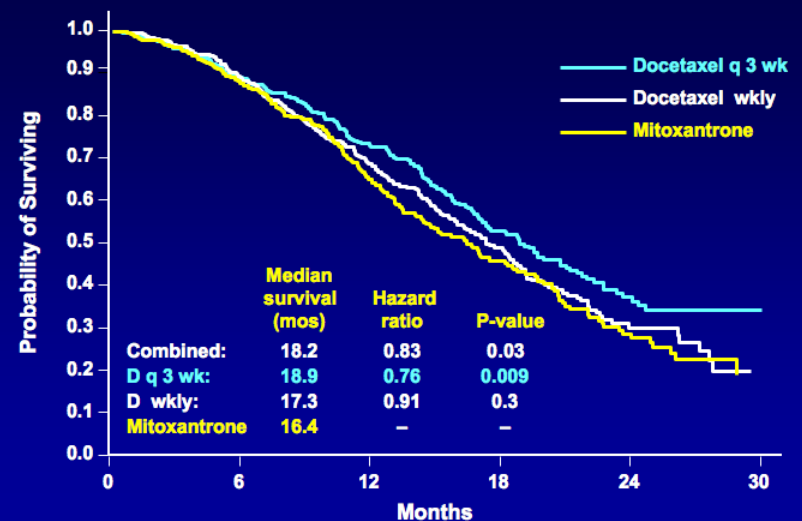
Docetaxel 30 mg/m<sup>2</sup> wkly  
5 of 6 wks +  
Prednisone 5 mg bid

Mitoxantrone 12 mg/m<sup>2</sup>  
q 3 wk +  
Prednisone 5 mg bid

Treatment duration in all 3 arms = 30 wks

Eisenberger et al. *Proc ASCO*. 2004;23:2. Abstract 4.

## TAX 327: Overall Survival



Eisenberger et al. *Proc ASCO*. 2004;23:2. Abstract 4.

# Why Not High-Dose Bicalutamide?

Bicalutamide at 150 mg/day proved to be just modestly effective for patients with androgen-independent prostate cancer; in particular, patients previously treated with long-term flutamide had a minimal benefit, thus indicating that previous antiandrogen therapy alters the response to subsequent hormonal agents<sup>1</sup>

At daily doses >200 mg, there is evidence of non-linearity of plasma concentrations, and therefore further benefit is unlikely to be seen as a result of further escalating the dose of bicalutamide<sup>2</sup>

1. Joyce R, et al. *J Urol*. 1998;159(1):149-153.

2. Blackledge GR. *Urology*. 1996;47(1A Suppl):44-7; discussion 48-53.

# Why Not Ketaconazole?

**Ketaconazole is a non-specific and weak inhibitor of CYP17**

**It has modest antitumor activity in castration-resistant prostate cancer, and its utility has been limited by its toxicities. Furthermore, an increase in androgenic steroids at disease progression on this agent indicates incomplete target blockade<sup>1</sup>**

# What About Sipuleucel-T Vaccine?

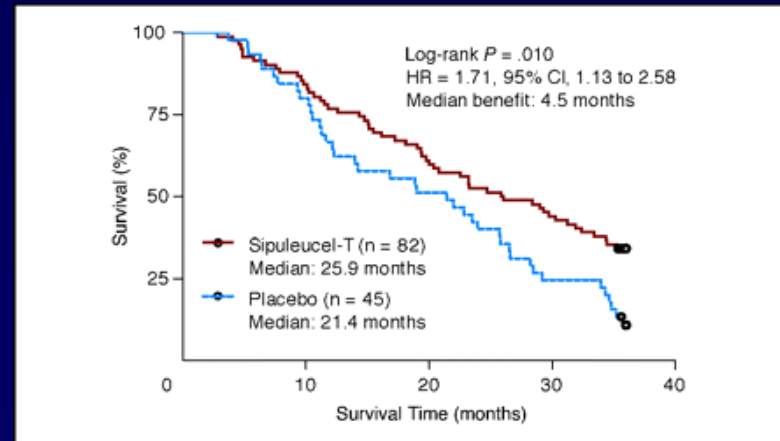
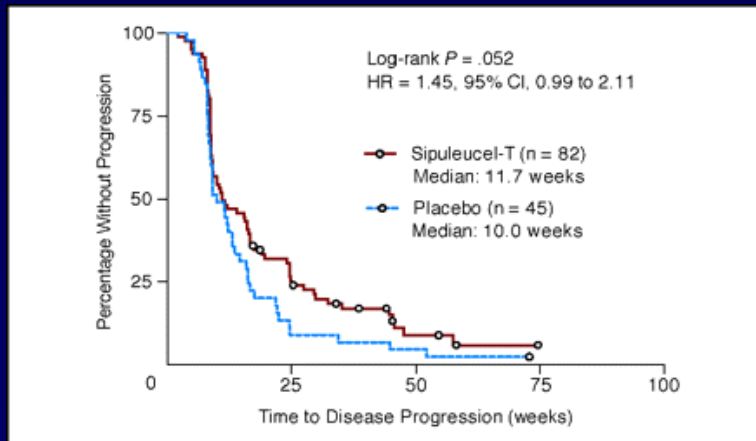
Sipuleucel-T is a cell-based vaccine composed of autologous Ag-presenting peripheral blood mononuclear cells (enriched for a dendritic cell fraction) that have been exposed to a recombinant protein consisting of granulocyte macrophage colony-stimulating factor (GM-CSF) fused to prostatic-acid phosphatase (PAP); upon administration, the vaccine may stimulate an antitumor T-cell response against tumor cells expressing PAP

Two randomized, double-blind, placebo-controlled, phase III trials (D9901 and D9902A) were conducted in men with advanced prostate cancer

# Sipuleucel-T Vaccine: Controversial Results

In the first trial (D9901), even though the improvement in the primary endpoint time to progression (TTP) did not reach statistical significance...

... a significant overall survival (OS) advantage in asymptomatic patients with HRPC was evidenced



# Sipuleucel-T Vaccine: Still Under Evaluation

In an integrated analysis of the D9901 and D9902A studies, patients randomized to sipuleucel-T demonstrated a 33% reduction in the risk of death (HR = 1.50; 95% CI = 1.10 - 2.05;  $P = .011$ )

The treatment effect remained strong after performing adjustments for imbalances in baseline prognostic factors, poststudy treatment chemotherapy use, and non-prostate cancer-related deaths

Additional support for the activity of sipuleucel-T was provided by the correlation between a measure of sipuleucel-T potency, ie, CD54 up-regulation, and OS

# Case Report (Continued)

- **Patient was enrolled in a clinical trial of abiraterone acetate and prednisolone**
- **Initial PSA decrease and partial response in lymph nodes**
- **After 10 months of treatment, his PSA started rising again and CT scan confirmed lymph node progression**

# Options to Consider

- **Ketoconazole**
- **Sipuleucel-T vaccine**
- **Chemotherapy with docetaxel**
- **Clinical trial of docetaxel ± VEGF-trap aflibercept**
- **Clinical trial of docetaxel + placebo vs docetaxel + ZD4054 (endothelin A receptor antagonist)—  
ENTHUSE 33 trial**

# My Choice

- Ketoconazole
- Sipuleucel-T vaccine
- Chemotherapy with docetaxel
- Clinical trial of docetaxel  $\pm$  VEGF-trap aflibercept
- **Clinical trial of docetaxel + placebo vs docetaxel + ZD4054 (endothelin A receptor antagonist)—  
ENTHUSE 33 trial**

# Endothelins and Prostate Cancer

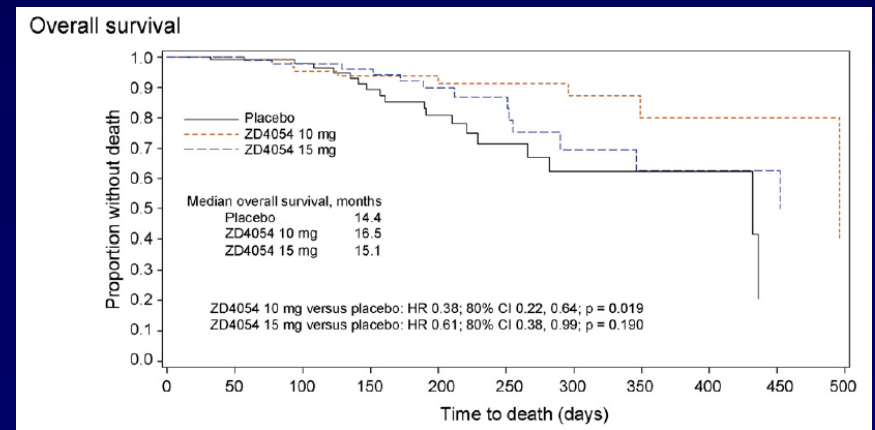
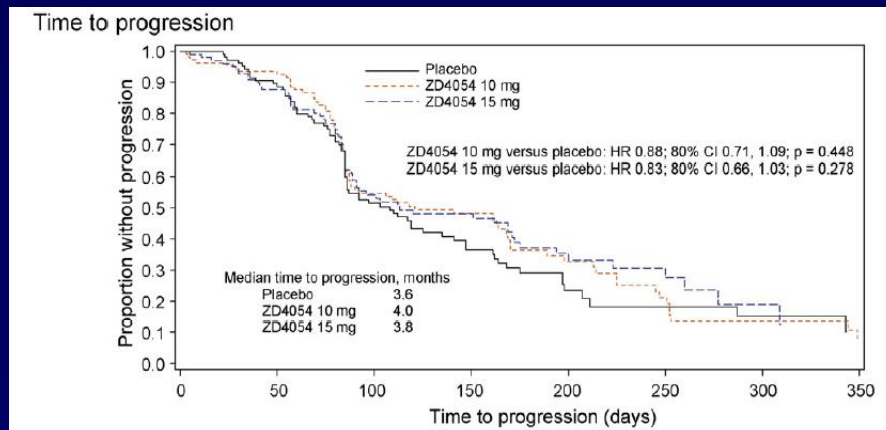
- The endothelin (ET) family consists of 3 potent paracrine/autocrine peptides (ET-1, -2, and -3), signaling through two G protein-coupled receptors: ETA and ETB
- ET-1, which is produced by prostate cancer cells, is mitogenic for both prostate cancer cells and for osteoblasts
- In prostate cancer, there is also an impairment of the ET-1 degradation pathway, resulting in a local increase in the concentration of ET-1
- Selective ETA-receptor antagonists have been shown to block ET-1-mediated proliferative effects in both prostate cancer cells and osteoblasts

# ZD4054 in Prostate Cancer

A double-blind, placebo-controlled, randomized, phase II trial in patients with HRPC and bone metastases who were pain free or mildly symptomatic for pain was thus performed

While the improvement in the primary endpoint TTP did not achieve statistical significance ...

...OS differences reached statistical significance



# Another Credible Option

- Ketoconazole
- Sipuleucel-T vaccine
- Chemotherapy with docetaxel
- **Clinical trial of docetaxel ± VEGF-trap aflibercept**
- **Clinical trial of docetaxel + placebo vs docetaxel + ZD4054 (endothelin A receptor antagonist)—  
ENTHUSE 33 trial**

# VEGF Trap

Among different strategies pursued to inhibit VEGF signalling, there are:

- MoAbs targeting VEGF-A (a)
- MoAbs or small molecules targeting the VEGF receptors (b, c)
- Aptamers that bind the heparin-binding domain of VEGF165 (pegaptanib) (e)
- Chimaeric soluble receptors such as the VEGF-trap (domain 2 of VEGFR-1 and domain 3 of VEGFR-2 fused to a Fc fragment of an antibody) (d)

