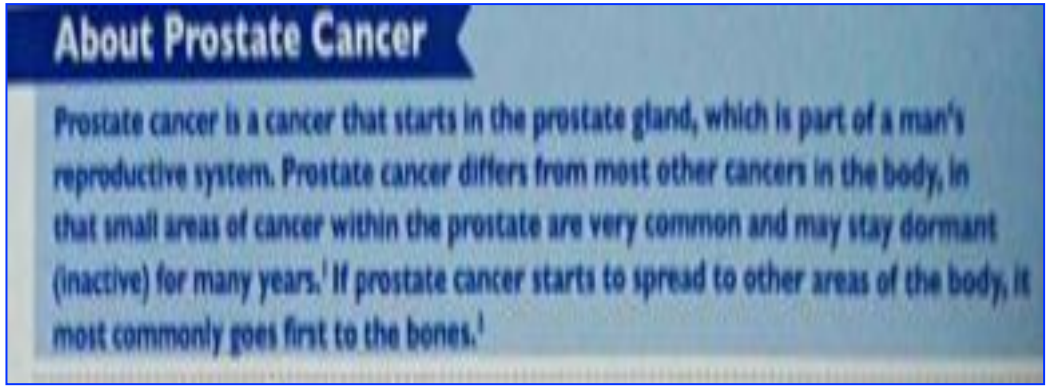
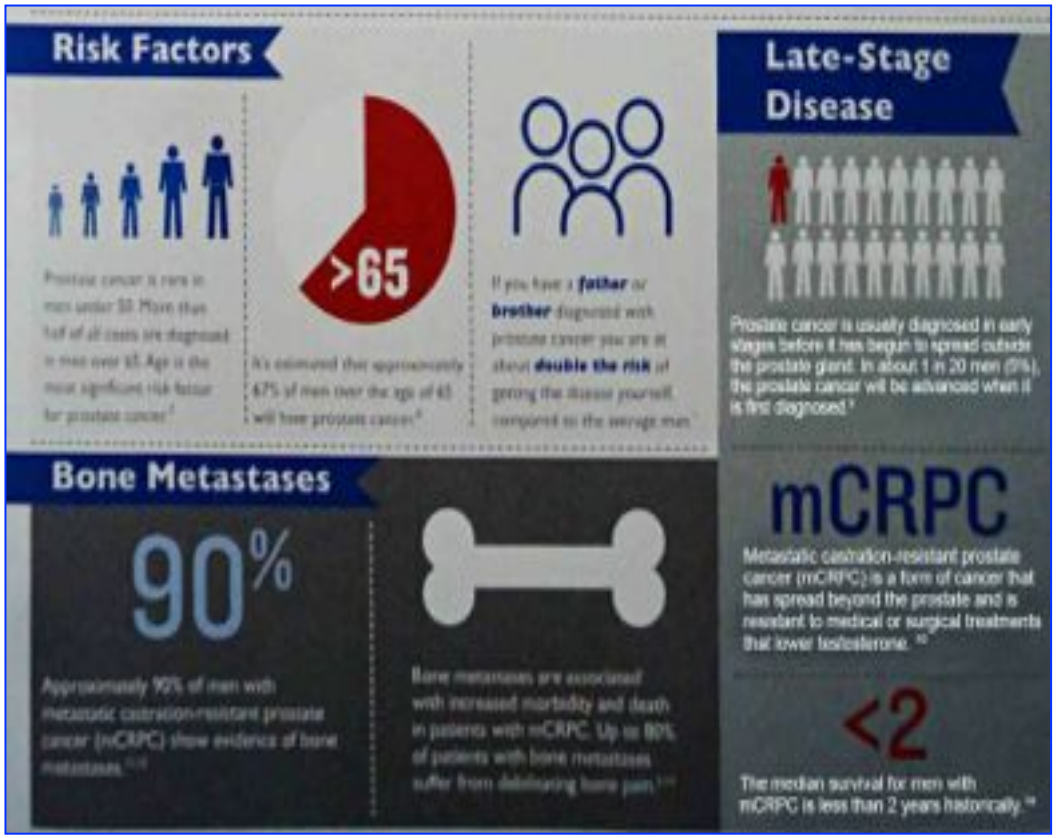
Nuove terapie post-ADT nel Carcinoma Prostatico Metastatico Resistente alla Castrazione

Hot topics nella pratica clinica

Beatrice Detti. Radioterapia Oncologica, AOU Careggi, Firenze.





Europe: estimated 417000 newly cases and 82000 deaths in 2014.

The number of deaths has declined an average of 3.3% each year, over the last 10 ys, with an increase in the 5-year survival from 66% to 99.6% from 1970s to today.

The reasons: increase in screening, earlier detection, treatment of less advanced disease, newer and more tolerable drugs.

Impact of news drugs in the median overall survival of patients with metastatic castration resistant prostate cancer (mCRPC)

N. Chaumard-Billotey [1], M. Aitichou [1], S. Chabaud [2], H. Boyle [3], B. Favier [1], Y. Devaux [3], JP. Droz [3], A. Fléchon [3]

[1] Pharmacy department, [2] Biostatistical unit, [3] Department of Oncology - Centre Léon Bérard, 28 Rue Laennec, Lyon 69008, France.

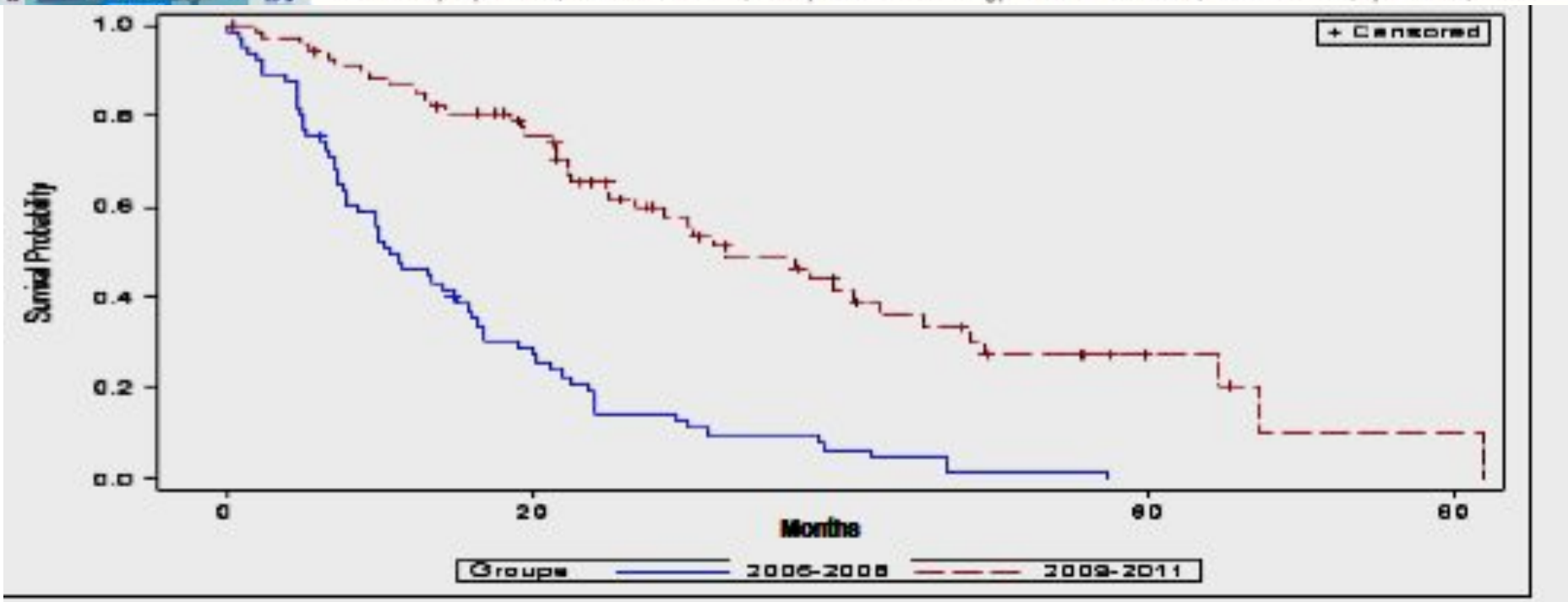


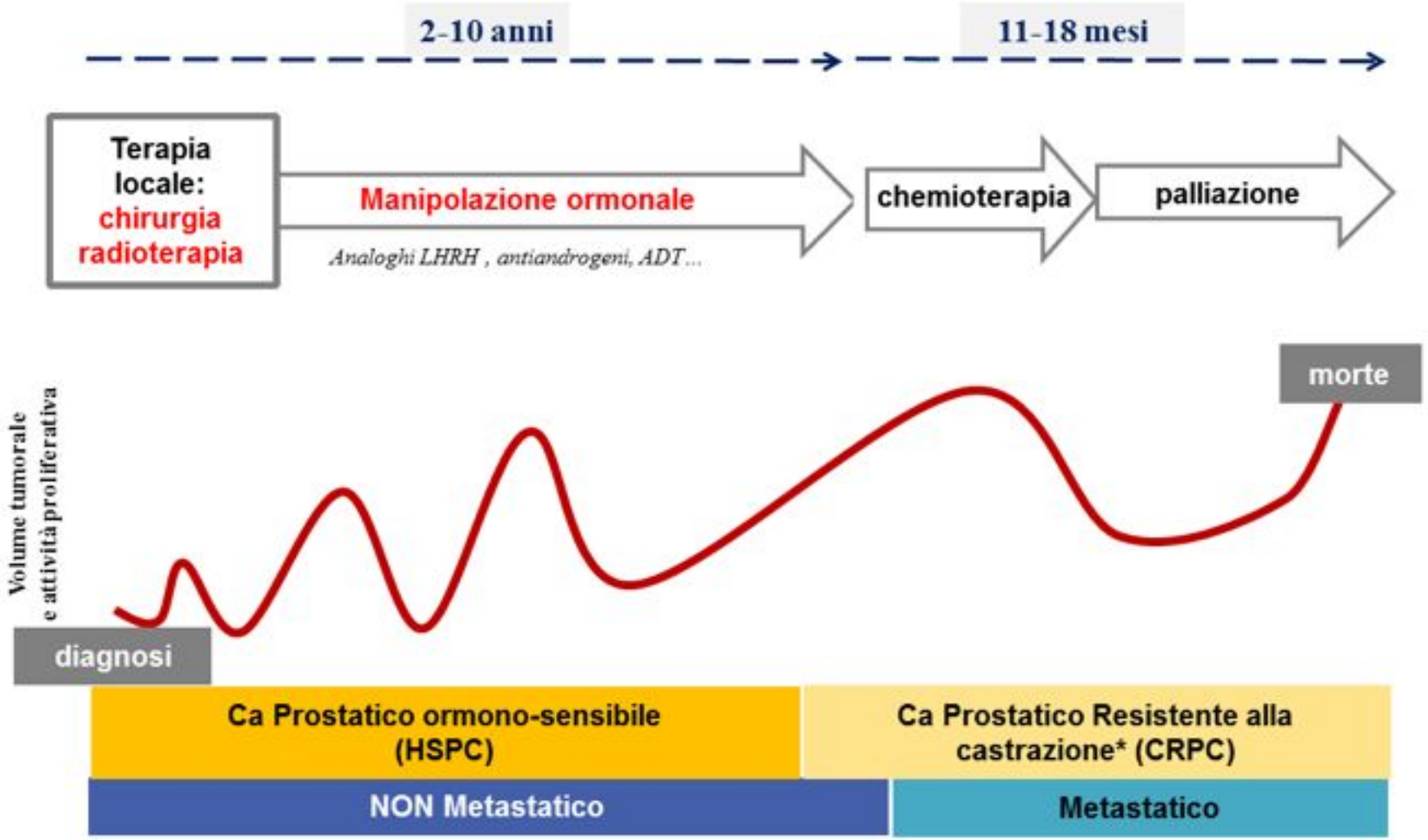
Figure 1 : Overall survival of mCRPC patients according to the period of treatment

Median OS was 10.6 months in group 1 (docetaxel-mitoxantrone) vs. 32.5 months in group 2 (Abiraterone, Cabazitaxel, Enzalutamide), $p<0.0001$.

At 12 months, OS rate was 46.4% in group 1 vs. 86.6% in group 2.

Chamaurd-Billotey et al, ECCO 2013

Schematizzazione decorso clinico del Carcinoma della Prostata

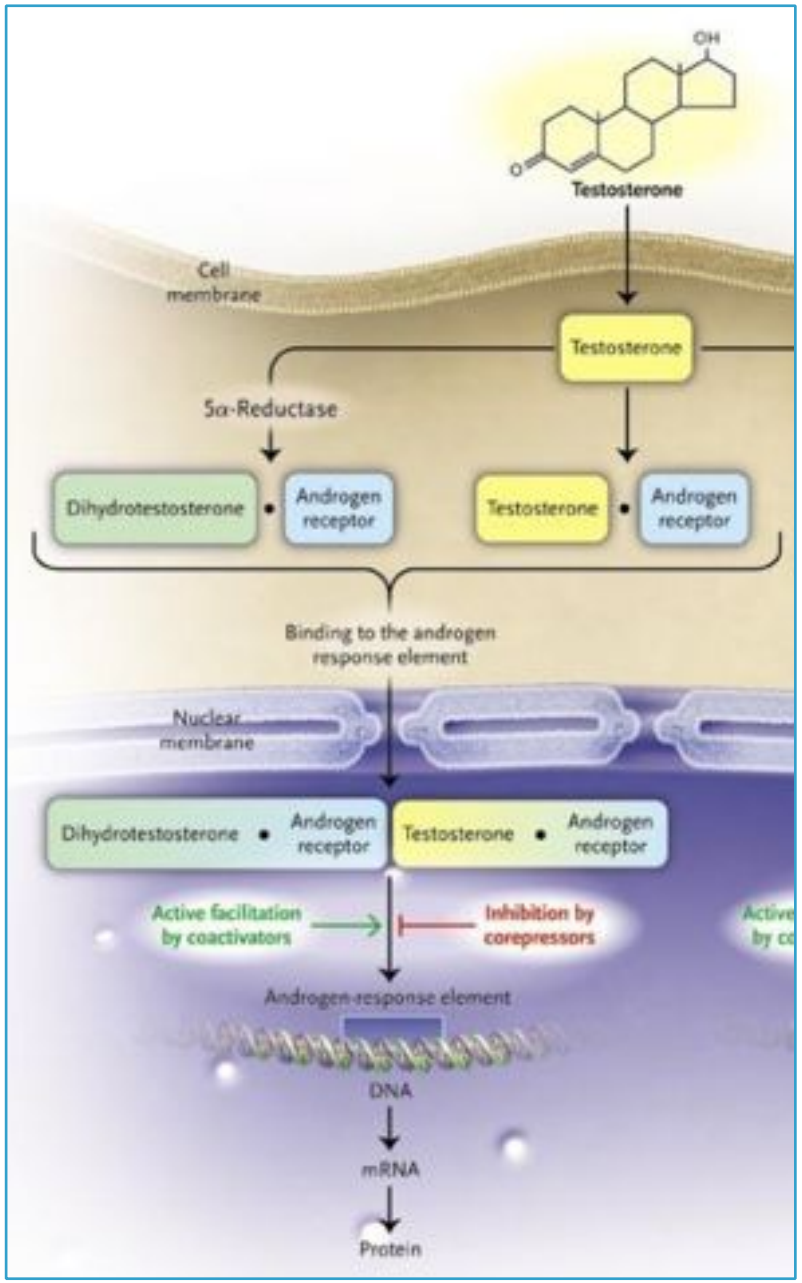


Mod. da Heidenreich et al., EAU Guidelines 2012

Il carcinoma della prostata è un classico esempio di tumore endocrino correlato

La crescita e la progressione tumorale sono alimentate dal testosterone e dipendono dai livelli di testosteronemia

Obiettivo terapia:
mantenere i livelli di testosteronemia sotto la soglia di castrazione (≤50 ng/dl)



Myth or Fact?

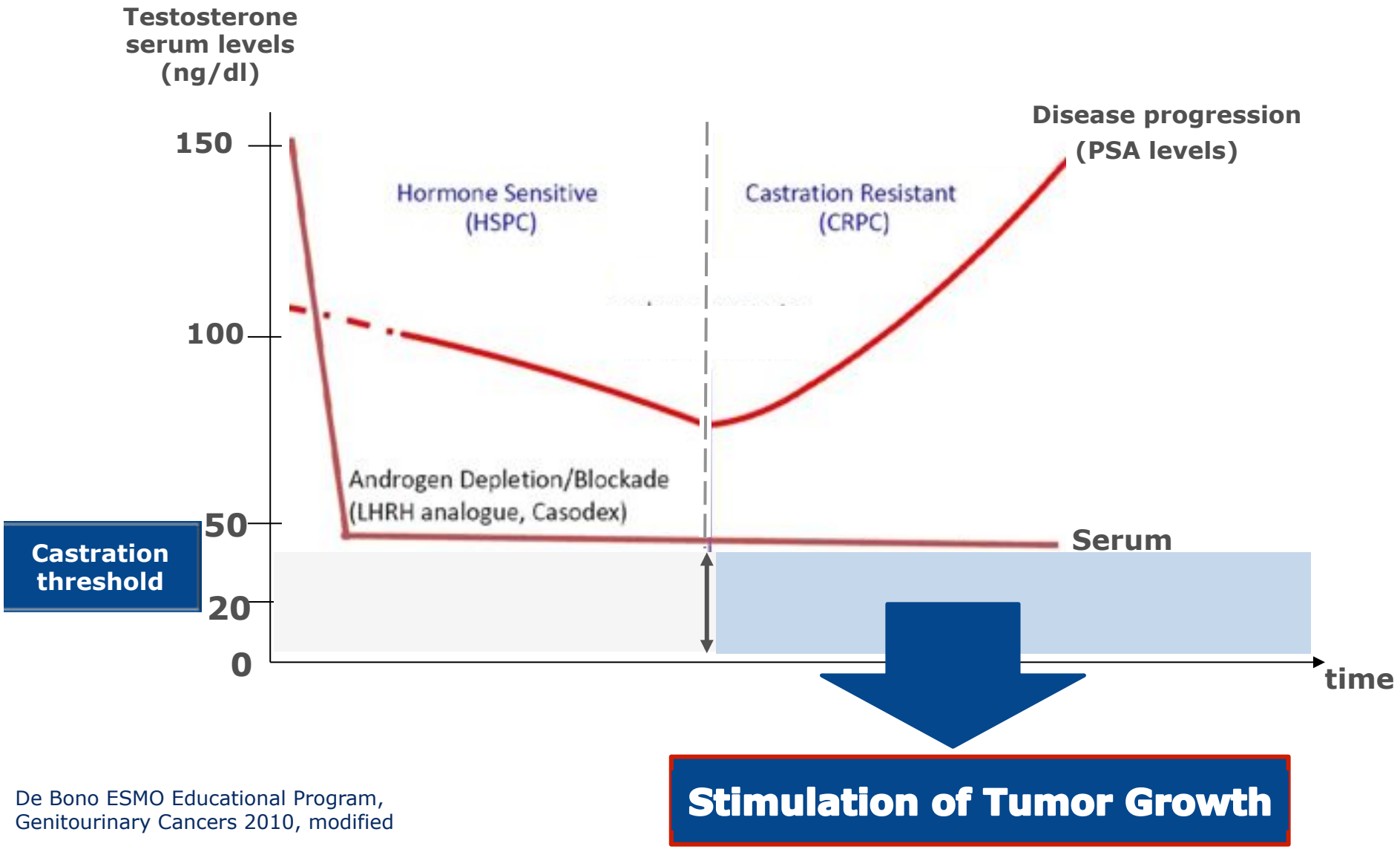
Myth

"….In metastatic hormone-resistant prostate cancer, tumor growth is no longer sensitive to androgen…."

Fact

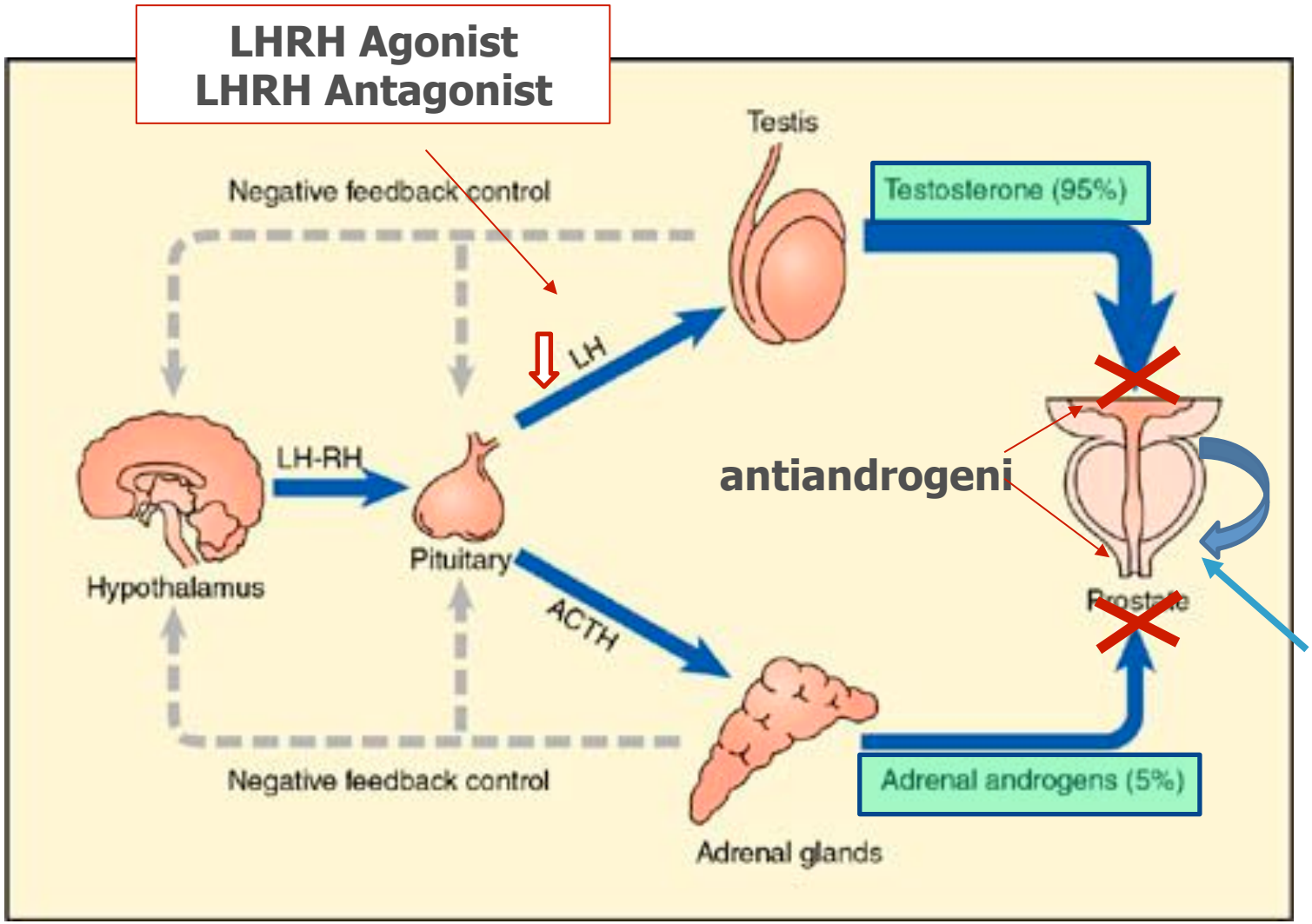
Metastatic castration-resistant prostate cancer remains androgen-sensitive, despite castrate levels of testosterone.

CASTRATE RESISTANT PROSTATE CANCER PATOPHYSIOLOGY



De Bono ESMO Educational Program, Genitourinary Cancers 2010, modified

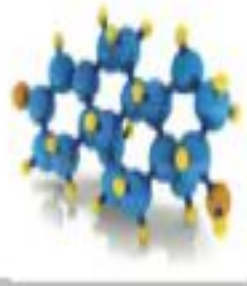
"mCRPC remains androgen-sensitive despite castrate levels of testosterone..."



In CRCP: Intracrine sinthesis of testosterone

Overexpression/ mutations of the receptor; ligand-independent activation; Up-regulation of the enzymes involved in androgen biosynthesis etc

Prostate and CRPC Steroidogenesis



Steroidogenesis in CRPC

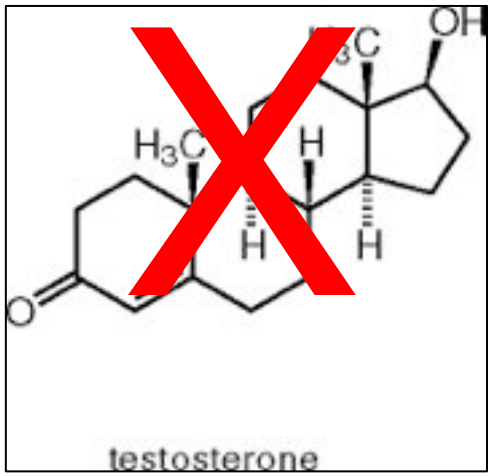
Tissue source	Testosterone ng/g (95% CI)*
Normal prostate cells	0.10 (0.00–0.26)
Benign prostatic hyperplasia cells	0.04 (0.00–0.24)
Prostate cancer cells	0.23 (0.03–0.44)
Metastatic prostate cancer tissue	0.74 (0.59–0.89)

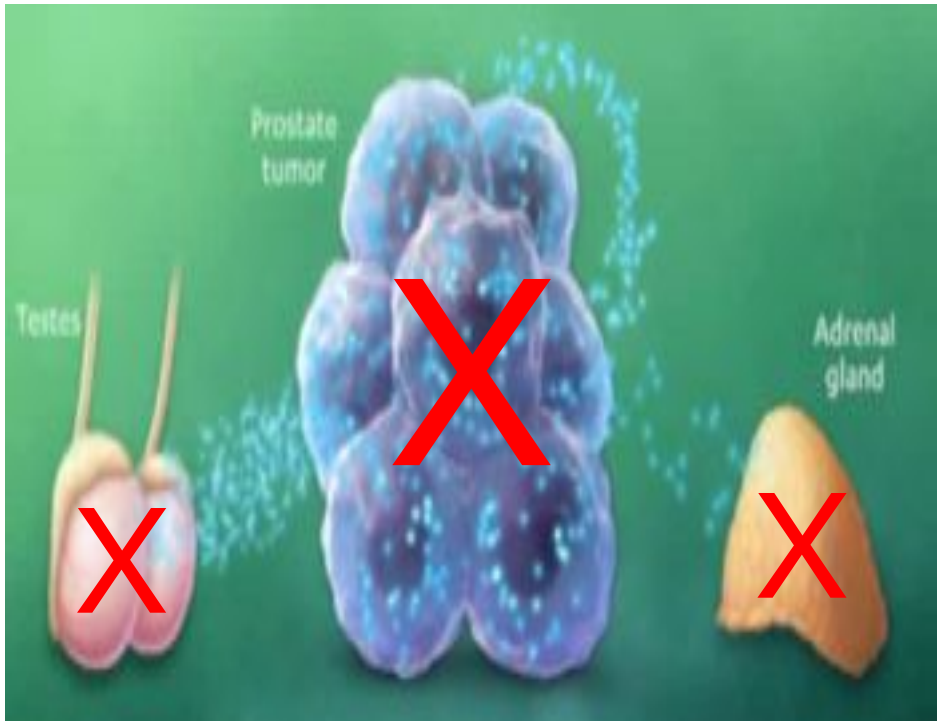
Mod. da Montgomery et al., Cancer Res 2008

mCRPC: "*take home message…*"

Nel mCRPC, anche piccole quantità di androgeni possono promuovere la crescita tumorale.

La riduzione/blocco della biosintesi di androgeni è una condizione fondamentale nella gestione ottimale del mCRPC.





Chen CD, et al. *Nat Med*. 2004.
Chen Y, et al. *Lancet Oncol*. 2009.

TABLE 1. Phase 3 Studies Demonstrating Improved Survival in Patients With Metastatic Castrate-Resistant Prostate Cancer

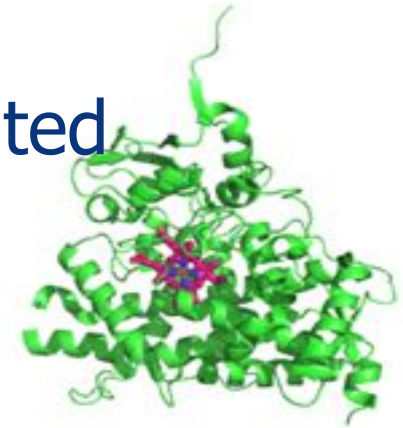
Regimens (Study Name)	Reference	Primary Endpoint	Notes
Docetaxel and prednisone vs mitoxantrone and prednisone (TAX-327)	Tannock 2004[3]	OS, 18.9 mo vs 16.5 mo (HR, 0.76; $P = .009$)	First phase 3 study to demonstrate a survival benefit in mCRPC
Sipuleucel-T vs placebo (IMPACT)	Kantoff 2010[5]	OS, 25.8 mo vs 21.7 mo (HR, 0.78; $P = .03$)	Accrual between August 2003 and November 2007; asymptomatic or minimally symptomatic; chemotherapy-naive or postchemotherapy
Cabazitaxel and prednisone vs mitoxantrone and prednisone (TROPIC)	de Bono 2010[4]	OS, 15.1 mo vs 12.7 mo (HR, 0.70; $P < .0001$)	Accrual between January 2007 and October 2008; progressive disease after docetaxel
Abiraterone and prednisone vs placebo and prednisone (COU-AA-301)	de Bono 2011[6]	OS, 14.8 mo vs 10.9 mo (HR, 0.65; $P < .001$)	Accrual between May 2008 and July 2009; progressive disease after docetaxel
Enzalutamide vs placebo (AFFIRM)	Scher 2012[8]	OS, 18.4 mo vs 13.6 mo (HR, 0.63; $P < .001$)	Accrual between September 2009 and November 2010; progressive disease after docetaxel; use of prednisone permitted but not required
Abiraterone and prednisone vs placebo and prednisone (COU-AA-302)	Ryan 2013[7]	OS, NYR vs. 27.2 mo (HR, 0.75; $P = .01$); rPFS, 16.5 mo vs 8.3 mo (HR, 0.53; $P < .001$)	Accrual between April 2009 and June 2010; chemotherapy-naive; asymptomatic or minimally symptomatic; no prior ketoconazole (≥7 d); patients with visceral metastases were excluded
Radium-223 vs placebo (ALSYMPCA)	Parker 2013[9]	OS, 14.0 mo vs 11.2 mo (HR, 0.70; $P = .002$)	Two or more bone metastases; no visceral metastases; postdocetaxel (or ineligible or unavailable); symptomatic disease
Enzalutamide vs placebo (PREVAIL)	Beer 2014[15]	OS, 32.4 mo vs 30.2 mo (HR, 0.70; $P < .0001$); rPFS, NYR vs 3.9 mo (HR, 0.19; $P < .0001$)	Accrual between September 2010 and September 2012; chemotherapy-naive; use of prednisone permitted but not required; no prior abiraterone or ketoconazole; asymptomatic or minimally symptomatic; patients with visceral disease (including liver or lung metastases) were eligible

Abiraterone: a novel therapeutic entity

- Mechanism of action: selective & irreversibile inhibitor of the enzyme CYP17A1 (17 αlfa-hydroxylase/C17,20 lyase), involved in biosynthesis of testosterone.

- First oral agent in this setting.

- Favorable profile of tolerability, with limited toxicities G 3-4.



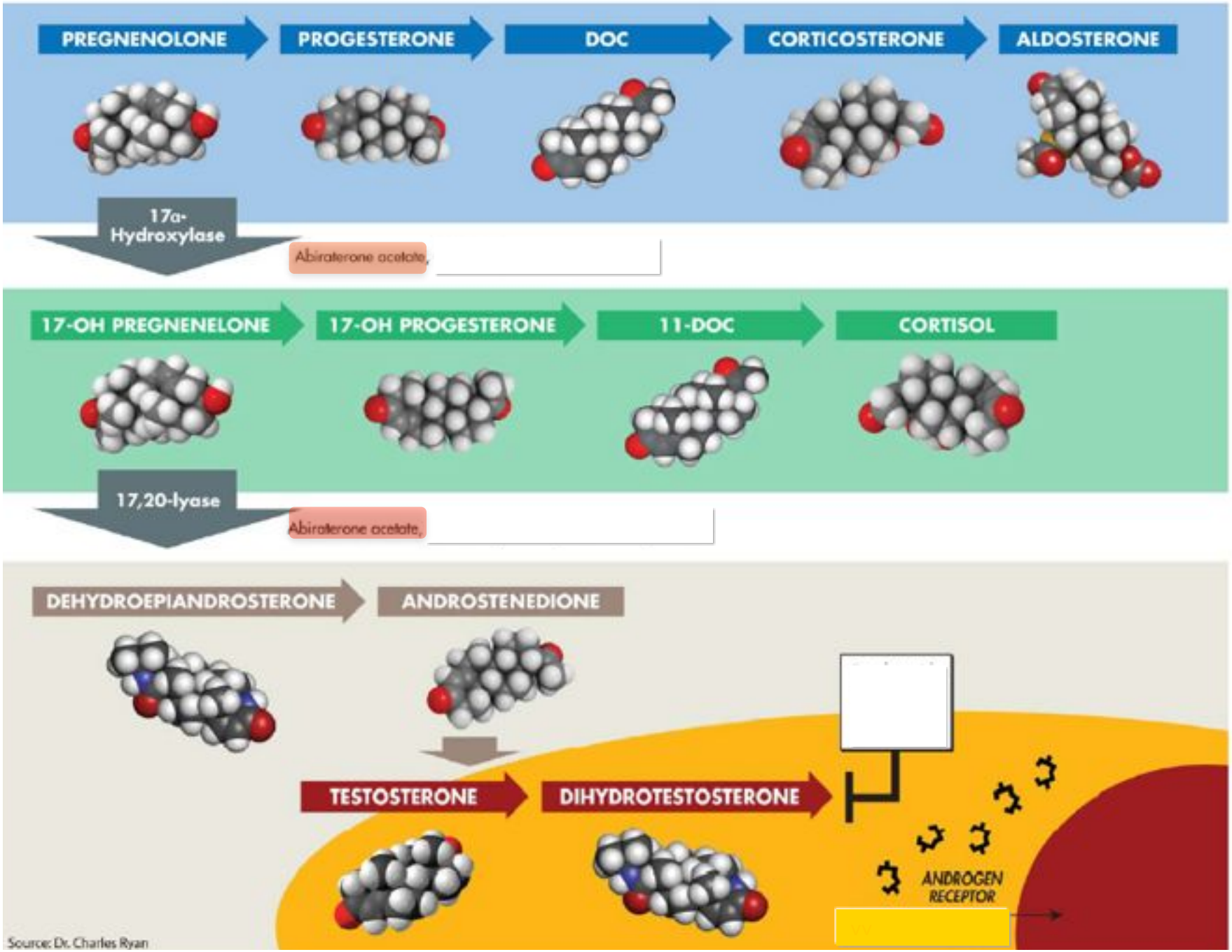
CYP17 A1

Steroidogenic enzymes in mCRPC

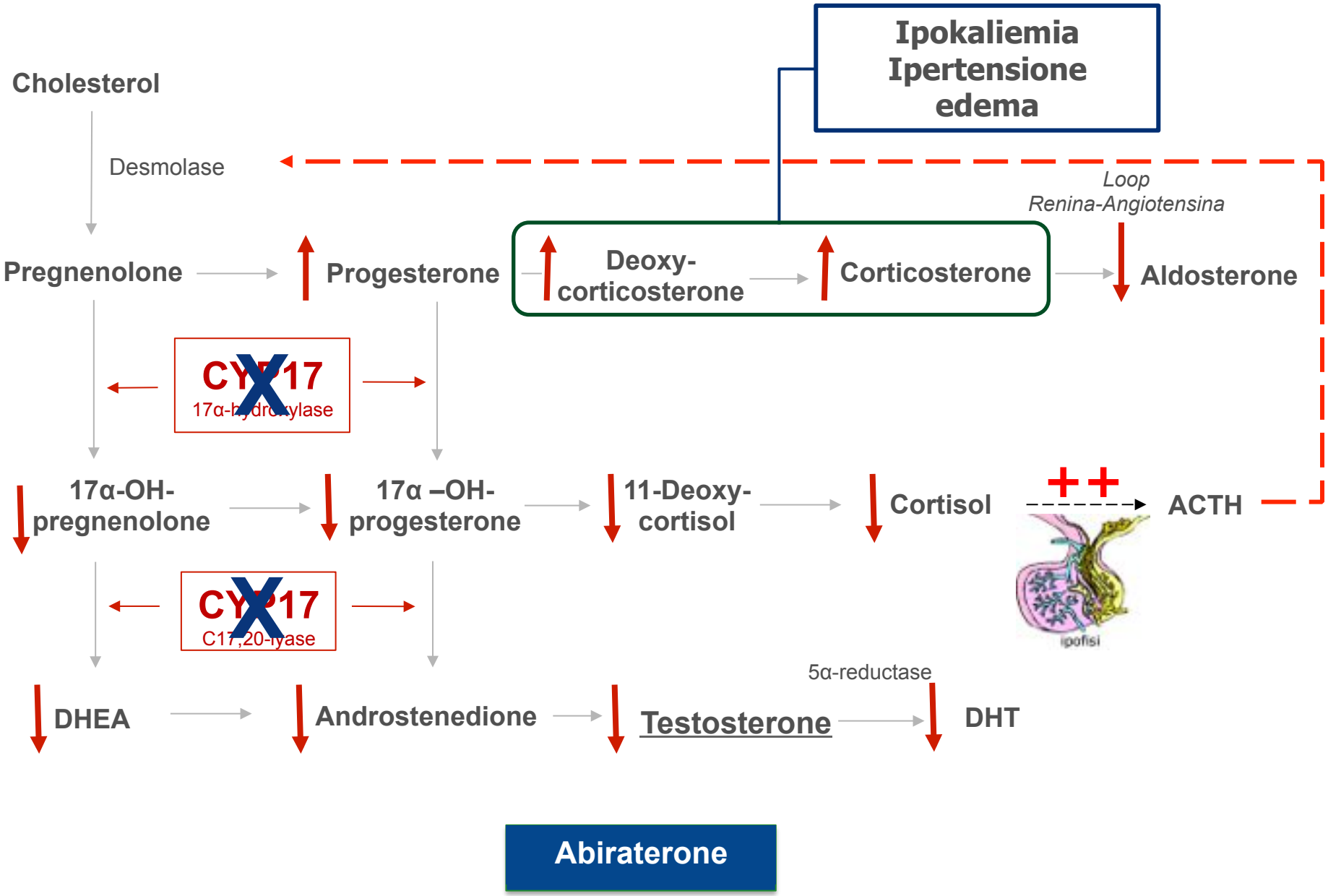
Table 2. Relative expression of steroidogenic enzymes in castration-resistant metastases versus primary prostate tumors

Gene	Fold change*	*P*
STAR	5.1	0.0105
FASN	9.6	0.0003
CYP11A	−1.1	0.8362
CYP17A	16.9	0.0005
3BHSD1	8.5	<0.0001
3BHSD2	7.5	0.0091
17BSHD2	8.2	0.0137
17BHSD3	8.7	<0.0001
17BHSD4	4.8	0.0019
AKR1C1	2.7	0.0601
AKR1C2	1.1	0.7895
AKR1C3 †	8.0	0.0026
SRD5A1	2.63	0.0050
SRD5A2	−9.4	0.0005
CYP19A1	30.3	<0.0001
UGT2B15	10.0	0.0779
UGT2B17	34.7	0.0013

Montgomery et al., Cancer Res 2008

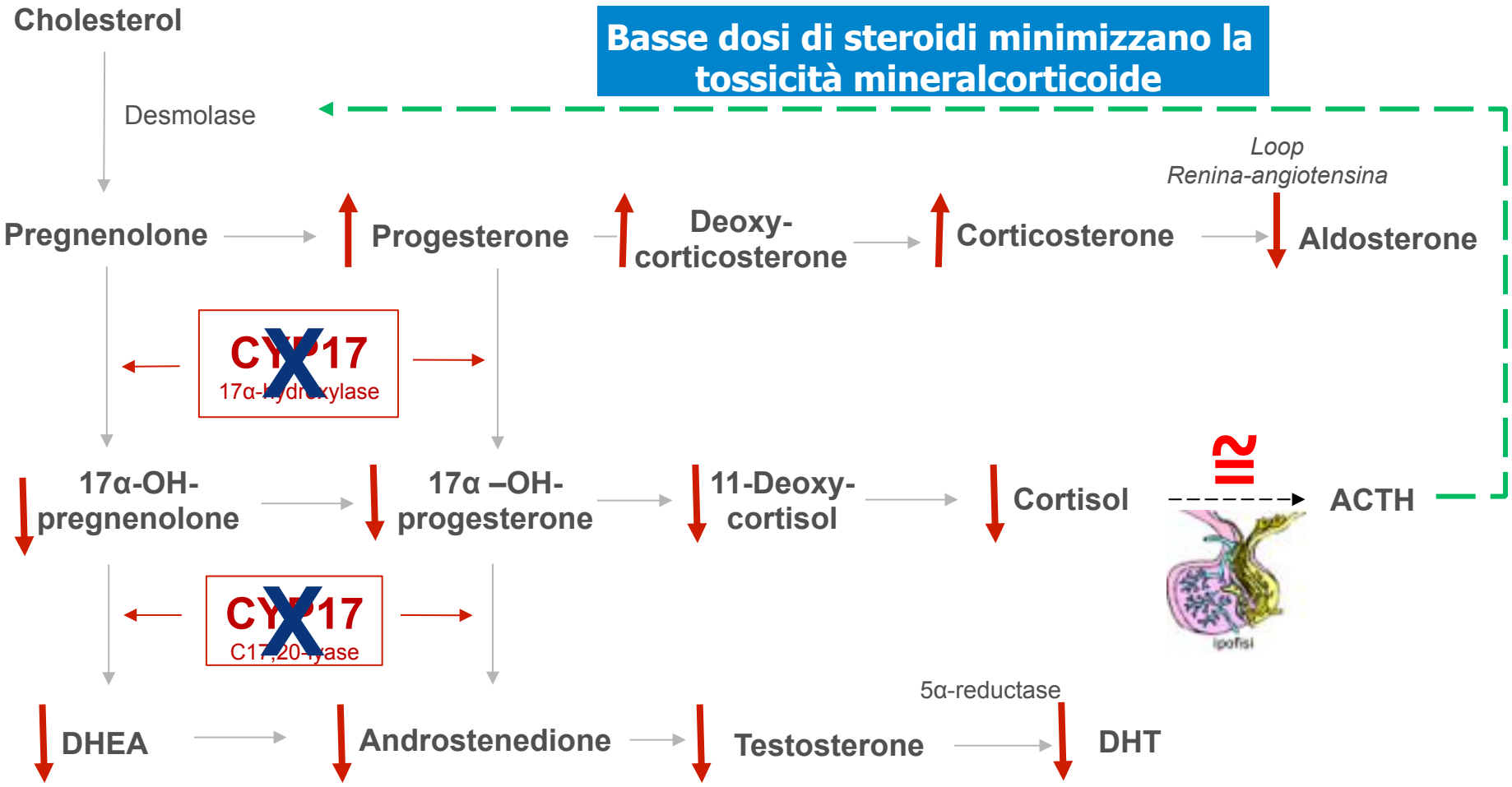

PREGNENOLONE
PROGESTERONE
DOC
CORTICOSTERONE
ALDOSTERONE
17α-Hydroxylase
Abiraterone acetate
17-OH PREGNENELONE
17-OH PROGESTERONE
11-DOC
CORTISOL
17,20-lyase
Abiraterone acetate
DEHYDROEPIANDROSTERONE
ANDROSTENEDIONE
TESTOSTERONE
DIHYDROTESTOSTERONE
ANDROGEN RECEPTOR
Source: Dr. Charles Ryan

Sintesi degli steroidi



Yang, Drugs. 2011; Attard, JCO 2008

Sintesi degli steroidi



Yang, Drugs. 2011; Attard, JCO 2008

Abiraterone: Sviluppo Clinico

- rPFS e OS
- Ritardare la comparsa del dolore
- Mantenere la QoL
- Ritardare l'inizio della CHT

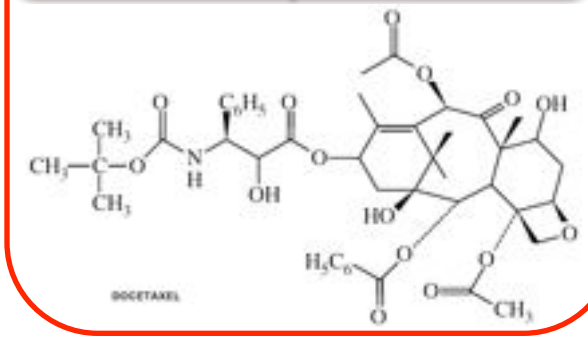
- Overall survival
- Ritardare i sintomi
- Mantenere la QoL

mCRPC
Pre-chemotherapy

Abiraterone
Study COU-AA 302[1]

APPROVED DECEMBER 2012

mCRPC
1st Line Chemotherapy
(Docetaxel)



mCRPC
Post-chemotherapy

Abiraterone
Study COU-AA 301[2]

APPROVED APRIL 2011

1. Ryan et al., N Engl J Med 2013;
2. De Bono et al., N Engl J Med 2011.

ABIRATERONE COU-AA-301 study

Patients*

- 1196 patients with progressive mCRPC
- Failed one or two chemotherapy regimens, one of which contained docetaxel

RANDOMISED 2:1

Abiraterone acetate
1000 mg daily
Prednisone 5 mg BID
***n* = 797**

Placebo daily
Prednisone 5 mg BID
***n* = 398**

Efficacy end points (ITT)

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

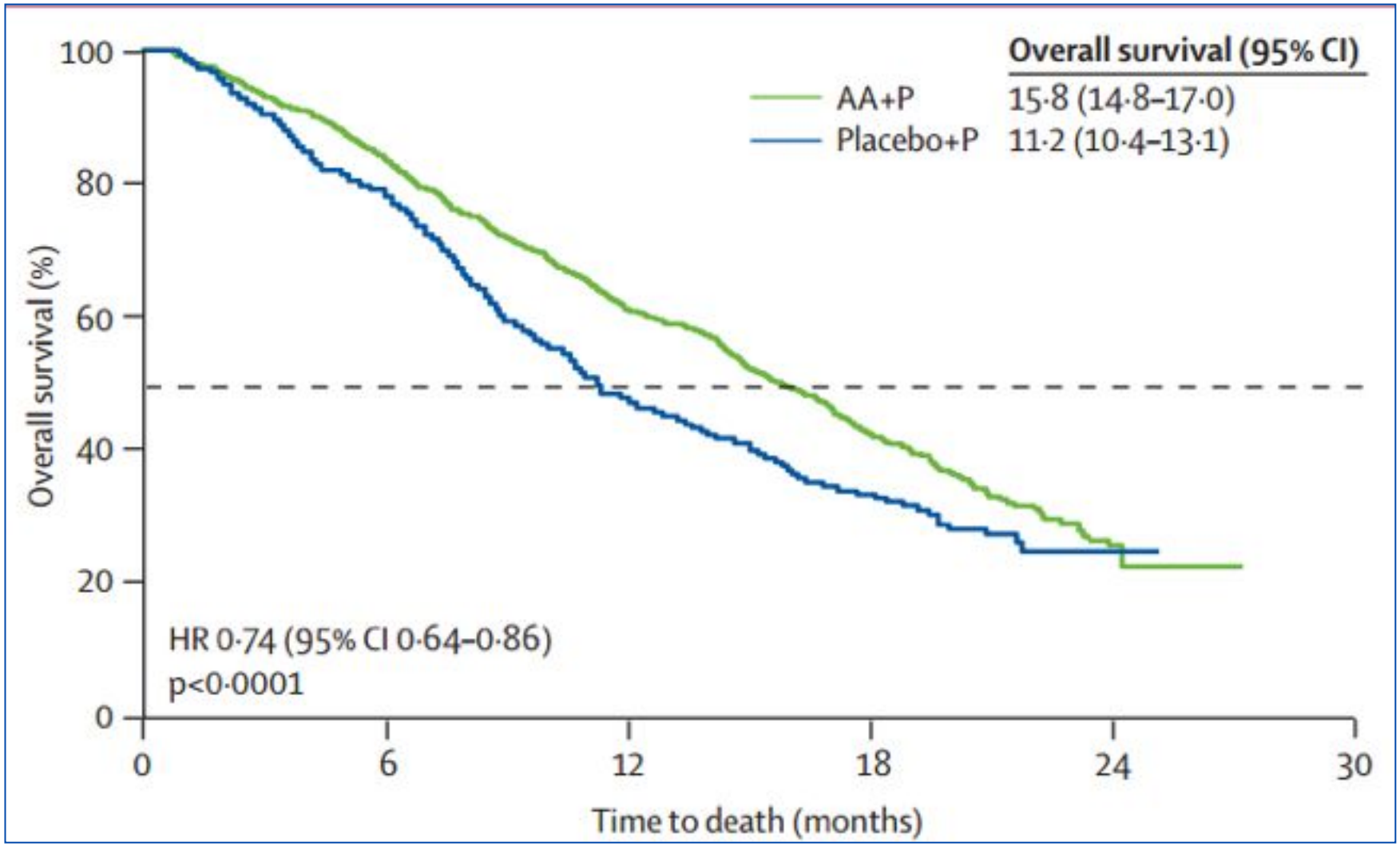
Secondary end point:
- TTPP
- rPFS
- PSA response

ABIRATERONE COU-AA-301 study

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Abiraterone Acetate (N=797)	Placebo (N=398)
Age		
Median (range) — yr	69 (42–95)	69 (39–90)
≥75 yr — no. of patients/total no. (%)	220/797 (28)	111/397 (28)
Disease location — no. of patients/total no. (%)		
Bone	709/797 (89)	357/397 (90)
Node	361/797 (45)	164/397 (41)
Liver	90/797 (11)	30/397 (8)
BPI-SF score for pain†		
No. of patients	792	394
Median score (range)	3.0 (0–10)	3.0 (0–10)
No. of previous cytotoxic chemotherapy regimens — no. of patients/total no. (%)		
1	558/797 (70)	275/398 (69)
2	239/797 (30)	123/398 (31)
ECOG performance status — no. of patients/total no. (%)		
0 or 1	715/797 (90)	353/398 (89)
2	82/797 (10)	45/398 (11)
Prostate-specific antigen		
No. of patients	788	393
Median (range) — ng/ml	128.8 (0.4–9253.0)	137.7 (0.6–10114.0)

ABIRATERONE COU-AA-301 study



Fizazi, Lancet Oncol 2012

COU-AA-301 study : Secondary end points

Variable	Abiraterone Acetate (N=797)	Placebo (N=398)	Hazard Ratio (95% CI)	P Value
Time to PSA progression (mo)	10.2	6.6	0.58 (0.46–0.73)	<0.001
Progression-free survival according to radiographic evidence (mo)	5.6	3.6	0.67 (0.59–0.78)	<0.001
PSA response rate (%)				
Total	38.0	10.1		<0.001
Confirmed response on the basis of the PSA concentration	29.1	5.5		<0.001
Objective response on the basis of imaging studies	14.0	2.8		<0.001

de Bono et al. N Engl J Med 2011

ABIRATERONE COU-AA-301 study

Event	Abiraterone Acetate (N=791)			Placebo (N=394)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	number (percent)					
Anemia	178 (23)	51 (6)	8 (1)	104 (26)	23 (6)	6 (2)
Thrombocytopenia	28 (4)	8 (1)	3 (<1)	13 (3)	1 (<1)	1 (<1)
Neutropenia	7 (1)	1 (<1)	0	1 (<1)	1 (<1)	0
Febrile neutropenia	0	0	0	0	0	0
Diarrhea	139 (18)	5 (1)	0	53 (14)	5 (1)	0
Fatigue	346 (44)	64 (8)	2 (<1)	169 (43)	36 (9)	3 (1)
Asthenia	104 (13)	18 (2)	0	52 (13)	7 (2)	1 (<1)
Back pain	233 (30)	44 (6)	3 (<1)	129 (33)	37 (9)	1 (<1)
Nausea	233 (30)	12 (2)	1 (<1)	124 (32)	10 (3)	0
Vomiting	168 (21)	13 (2)	1 (<1)	97 (25)	11 (3)	0
Hematuria	65 (8)	11 (1)	0	31 (8)	9 (2)	0
Abdominal pain	95 (12)	16 (2)	0	44 (11)	6 (2)	0
Pain in arm or leg	134 (17)	18 (2)	1 (<1)	79 (20)	20 (5)	0
Dyspnea	102 (13)	8 (1)	2 (<1)	46 (12)	7 (2)	2 (<1)
Constipation	206 (26)	8 (1)	0	120 (31)	4 (1)	0
Pyrexia	71 (9)	3 (<1)	0	35 (9)	5 (1)	0
Arthralgia	215 (27)	33 (4)	0	89 (23)	16 (4)	0
Urinary tract infection	91 (12)	17 (2)	0	28 (7)	2 (<1)	0
Pain	13 (2)	5 (1)	0	19 (5)	6 (2)	1 (<1)
Bone pain	194 (25)	42 (5)	2 (<1)	110 (28)	25 (6)	4 (1)

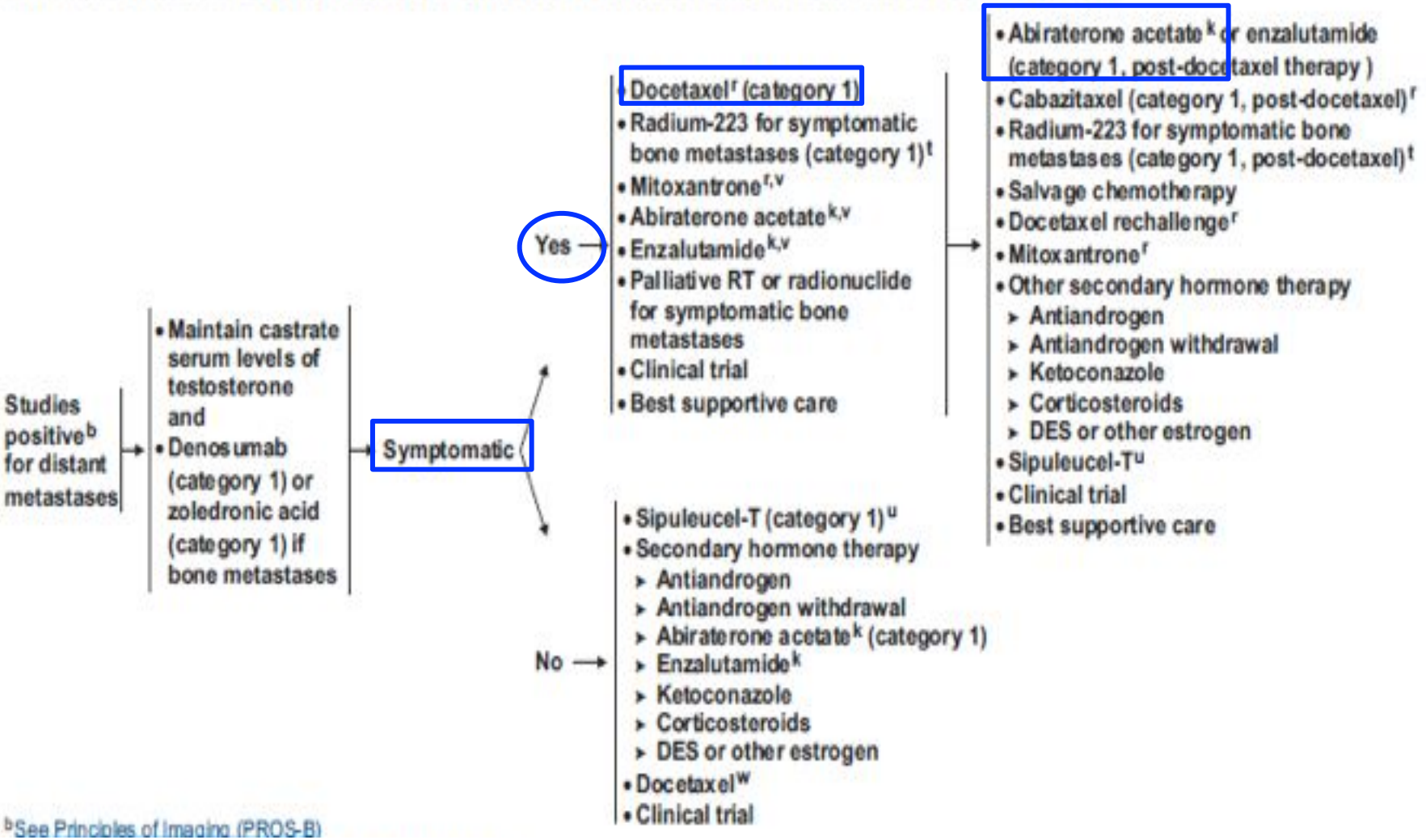
de Bono et al. N Engl J Med 2011

ABIRATERONE COU-AA-301 study

Event	Abiraterone Acetate (N=791)			Placebo (N=394)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	number (percent)					
Fluid retention and edema	241 (31)	16 (2)	2 (<1)	88 (22)	4 (1)	0
Hypokalemia	135 (17)	27 (3)	3 (<1)	33 (8)	3 (1)	0
Cardiac disorder*	106 (13)	26 (3)	7 (1)	42 (11)	7 (2)	2 (<1)
Liver-function test abnormalities	82 (10)	25 (3)	2 (<1)	32 (8)	10 (3)	2 (<1)
Hypertension	77 (10)	10 (1)	0	31 (8)	1 (<1)	0

de Bono et al. N Engl J Med 2011

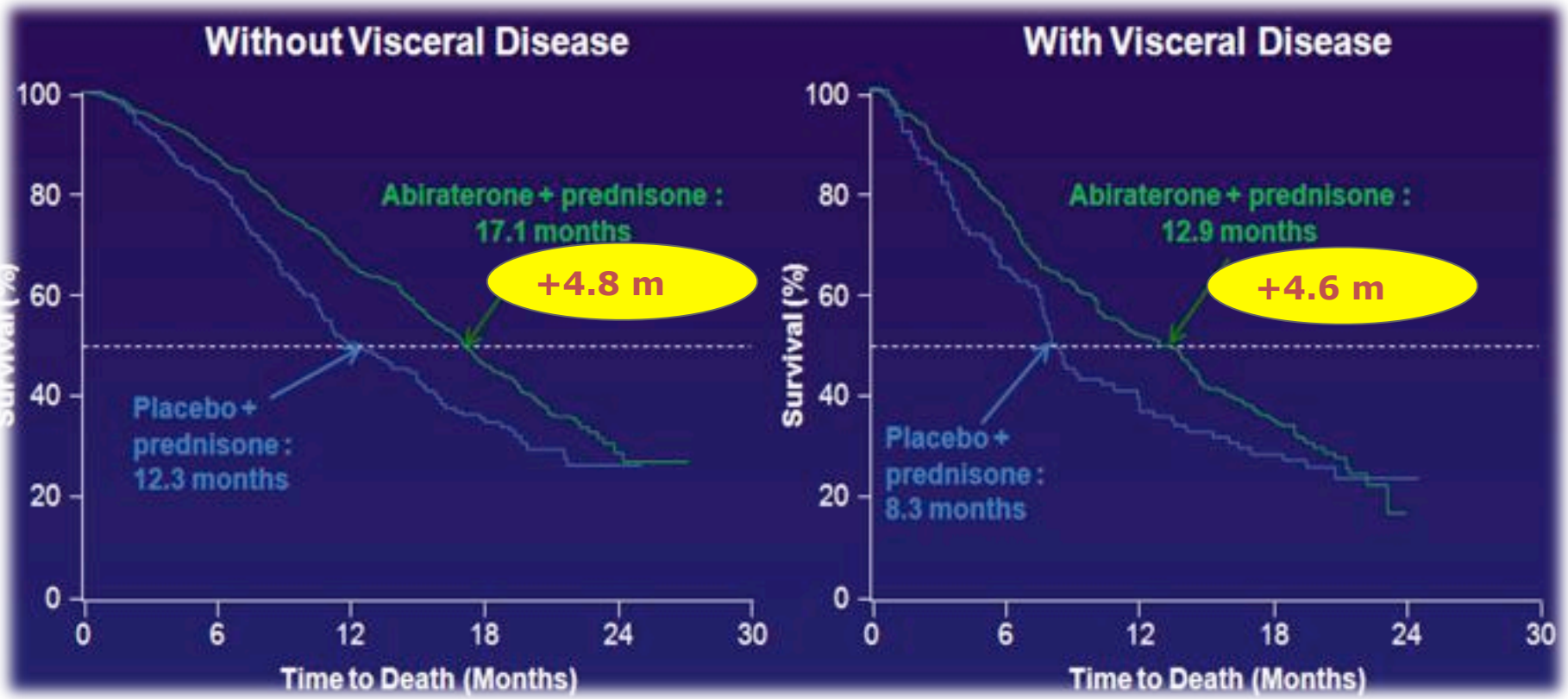
ADVANCED DISEASE: ADDITIONAL SYSTEMIC THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER



[b] See Principles of Imaging (PROS-B)

Nuove evidenze dallo studio COU-AA 301

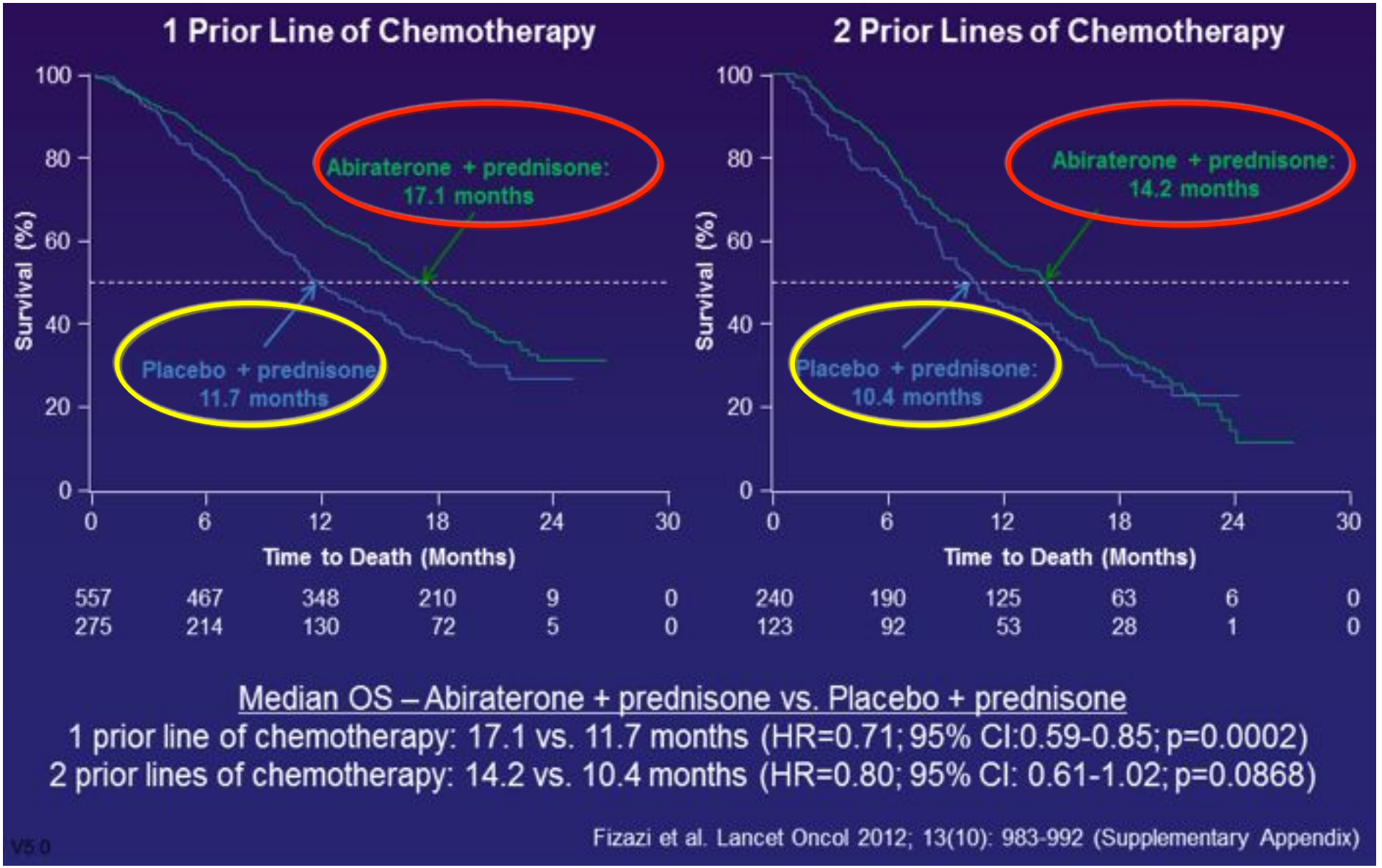
Exploratory analysis of the visceral disease subgroup in COU-AA-301 study



AA provides significant clinical benefit, including improvements in OS and secondary end points, in patients with or without baseline visceral disease. The presence of visceral disease does not preclude clinical benefit from abiraterone.

Goodman et al., Prostate Cancer and Prostatic Disease 2013

Exploratory analysis for subgroup with 1 or 2 prior lines of chemo, in COU-AA-301 study



Median OS – Abiraterone + prednisone vs. Placebo + prednisone

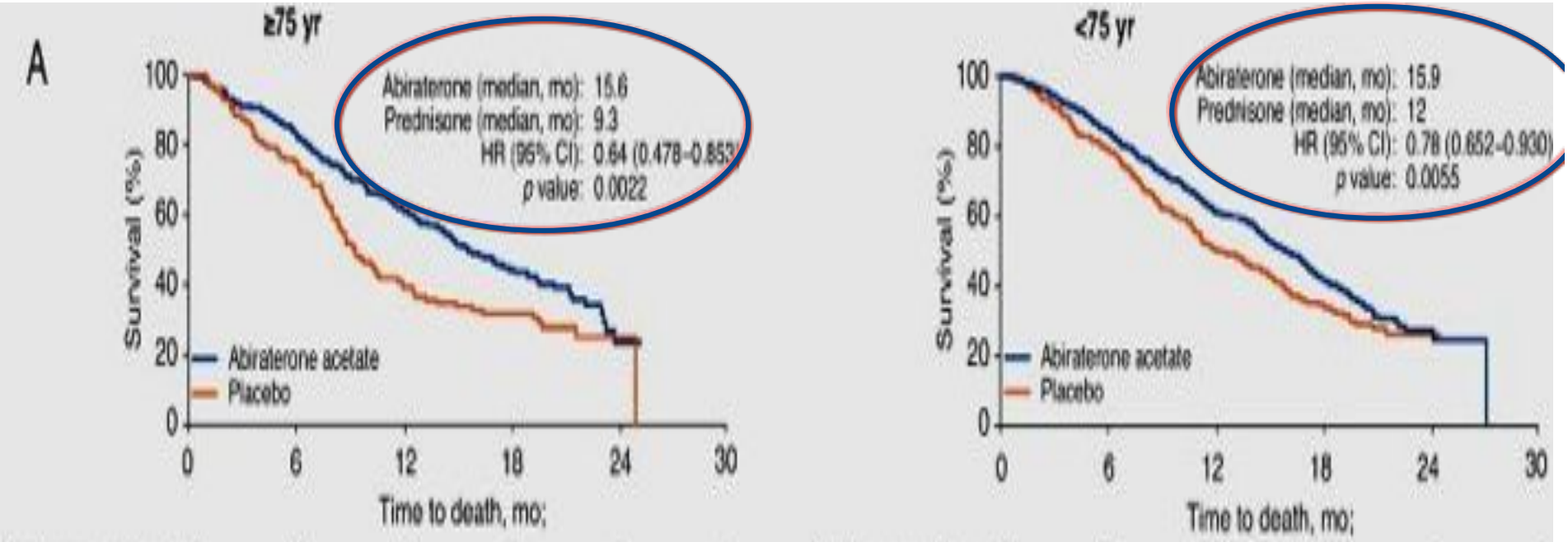
1 prior line of chemotherapy: 17.1 vs. 11.7 months (HR=0.71; 95% CI:0.59-0.85; p=0.0002)

2 prior lines of chemotherapy: 14.2 vs. 10.4 months (HR=0.80; 95% CI: 0.61-1.02; p=0.0868)

Fizazi et al. Lancet Oncol 2012; 13(10): 983-992 (Supplementary Appendix)

V5.0

Efficacy and Safety of Abiraterone Acetate in an Elderly Patient Subgroup (Aged 75 and Older)



Conclusions: AA improves OS and is well tolerated in both elderly patients and younger patients with mCRPC following docetaxel.

Mulders European Urology 2013

Am J Clin Oncol. 2013 Sep 21. [Epub ahead of print]

Safety of Abiraterone Acetate in Castration-resistant Prostate Cancer Patients With Concomitant Cardiovascular Risk Factors.

Procopio G[1], Grassi P, Testa I, Verzoni E, Torri V, Salvioni R, Valdagni R, de Braud F.

Author information

Abstract

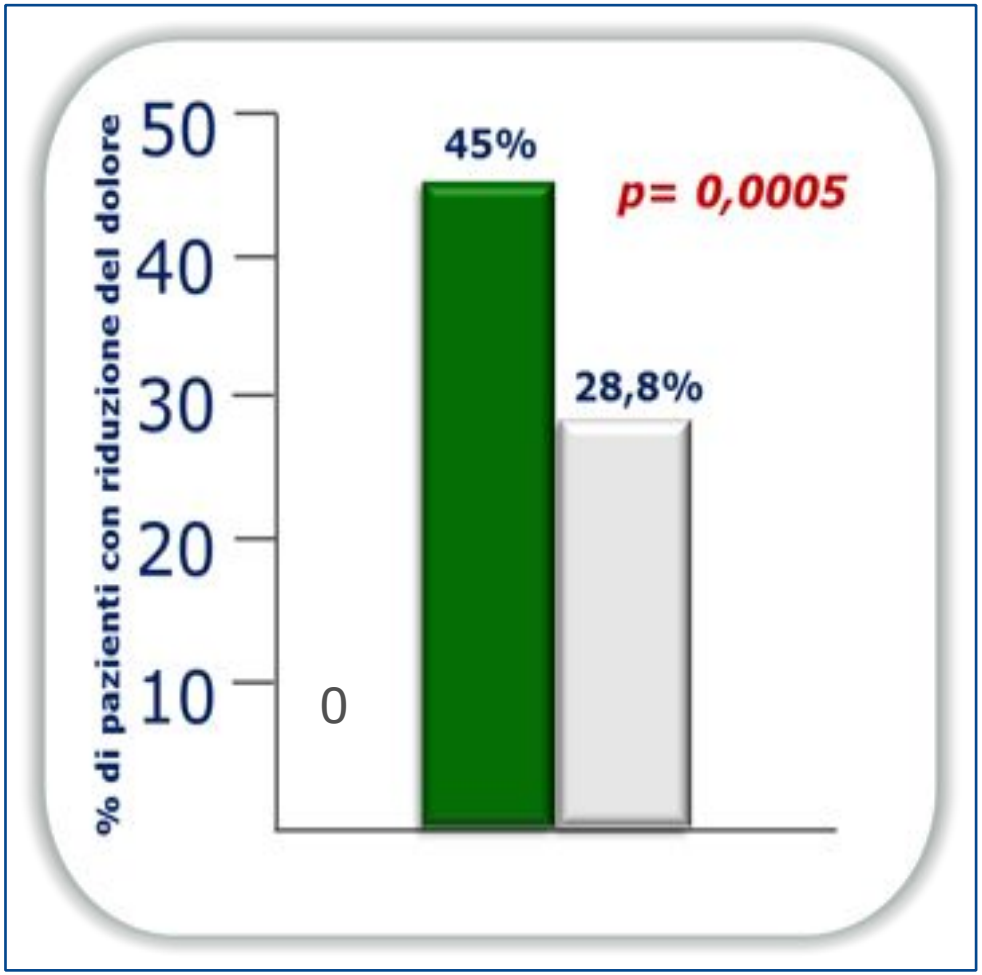
OBJECTIVES:: The aim of this study was to evaluate the safety profile of abiraterone acetate (AA) in metastatic castration-resistant prostate cancer (mCRPC) men with cardiovascular comorbidity, as little conclusive safety data are available in this patient subset.

PATIENTS AND METHODS:: A retrospective analysis of mCRPC patients with controlled cardiovascular comorbidities, receiving AA 1000 mg administered orally once daily and prednisone 5 mg twice daily, between April 2011 and July 2012, was performed. All clinical and instrumental variables and toxicity data were analyzed by descriptive statistics: mean, standard deviation, minimum and maximum values for continuous variables, and absolute and relative frequencies for categorical variables.

RESULTS:: A total of 51 mCRPC patients were evaluated. Metastatic sites included the bone (74%), lungs, and liver (26%). All patients were previously treated with at least 2 lines of hormone and 1 docetaxel-based chemotherapy. Preexisting cardiac risk factors included hypertension (41%), cardiac ischemia (12%), arrhythmias (6%), dislipidemia (18%), and hyperglycemia (30%). No grade 3-4 adverse events were observed. Grade 1-2 adverse events included fluid retention (18%), asthenia (15%), and hypertension (16%). Median progression-free survival was 5.1 months (95% confidence interval, 0.5-12). Prostate specific antigen assessment revealed a good overall disease control rate (64%).

CONCLUSIONS:: AA appears to be safe and well tolerated even in patients with cardiovascular comorbidities or with increased risk factors for cardiovascular diseases.

Effect of abiraterone acetate on pain control : exploratory analysis of data from the COU-AA-301

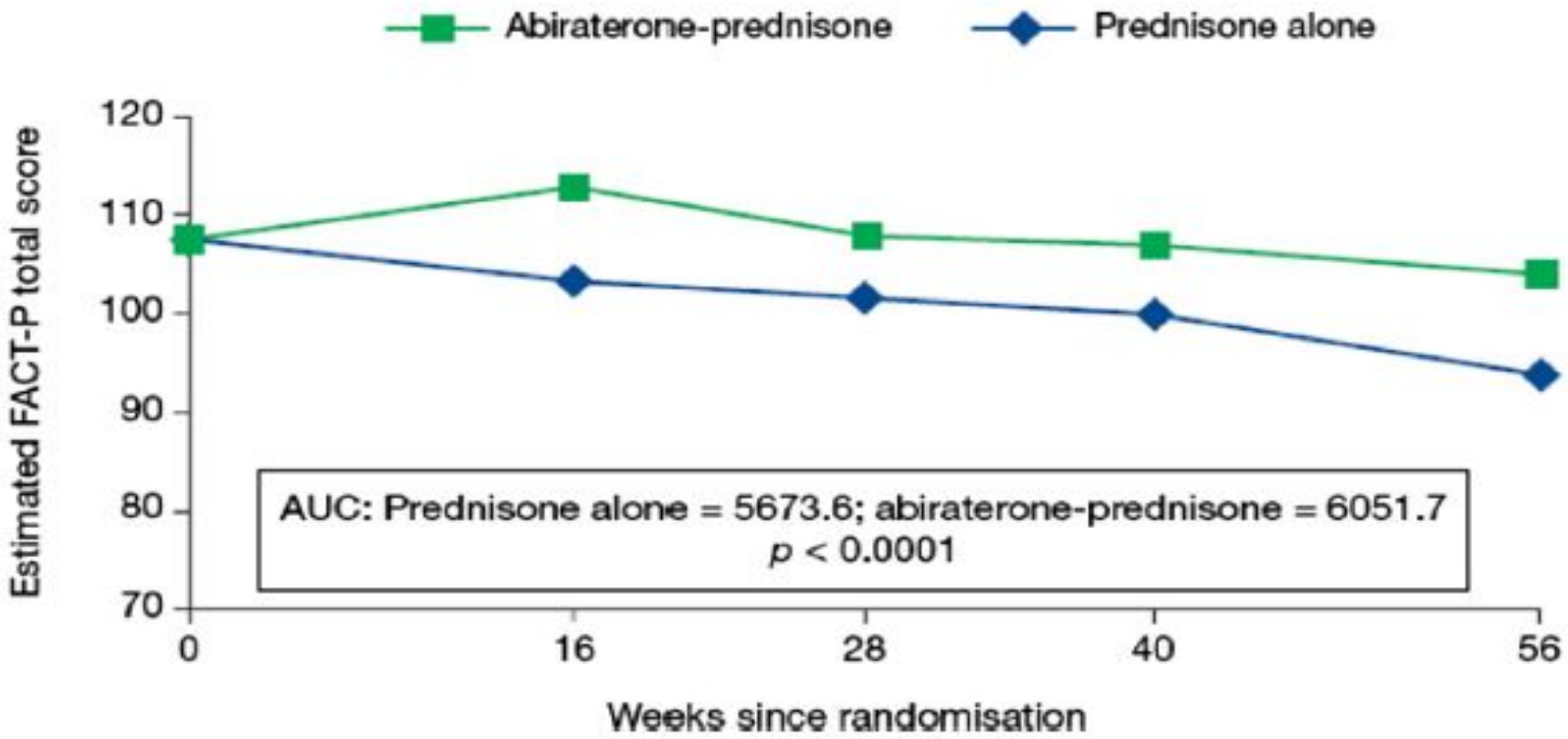


Abiraterone Acetato + prednisone
Prednisone + placebo

In patients with clinically significant pain at baseline, AA and prednisone resulted in significantly more palliation (45% vs 28.8%) and faster palliation (median time to palliation 5.6 months vs 13.7 months).

Logothetis et al, *Lancet Oncol* 2012

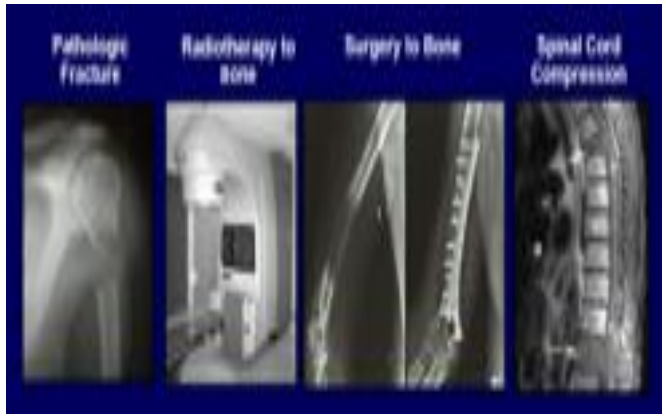
Effect of abiraterone acetate treatment on the quality of life



Conclusions: The previously demonstrated survival benefit for abiraterone is accompanied by improvements in patient-reported HRQoL and a significant delay in HRQoL deterioration.

Harland, European Journal of Cancer 2013

Effect of AA on skeletal-related Events: exploratory analysis of data from the COU-AA-301



Median time to occurrence of first SRE was significantly longer with AA vs placebo (25 months vs 20.3 months, p=0·0001).

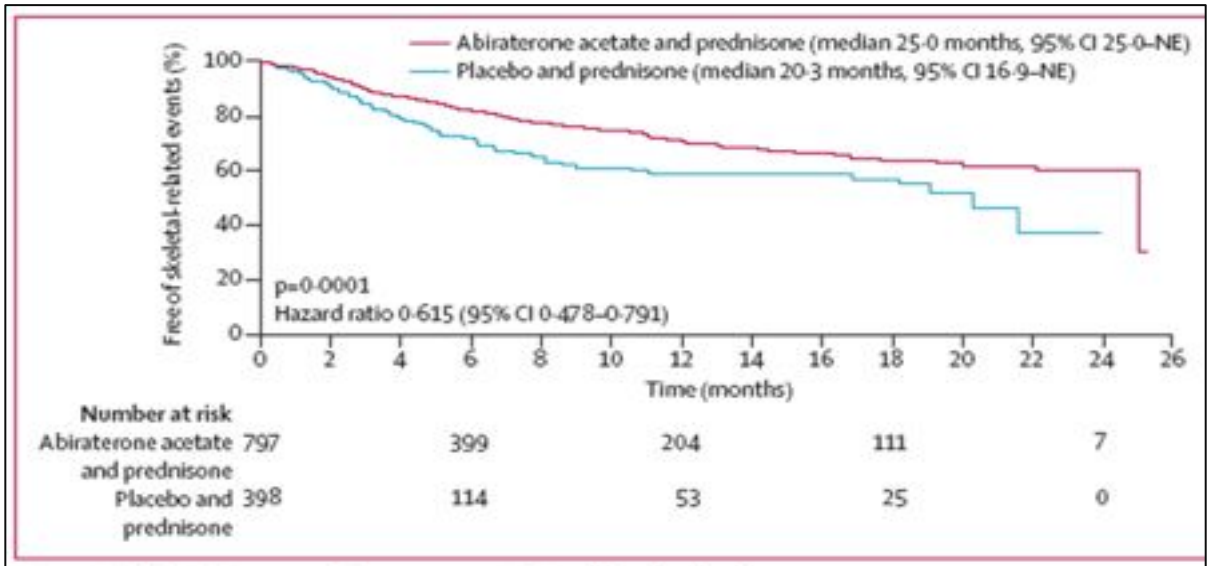


Figure 4: Kaplan-Meier curves for occurrence of first skeletal-related event
p values were obtained from log-rank tests stratified by Eastern Cooperative Oncology Group performance status score (0–1 vs 2), pain score (absent vs present), number of previous chemotherapy regimens (1 vs 2), and type of progression (prostate-specific antigen only vs radiographic plus prostate-specific antigen). Lines for each curve end at the last available observation. NE=not estimable.

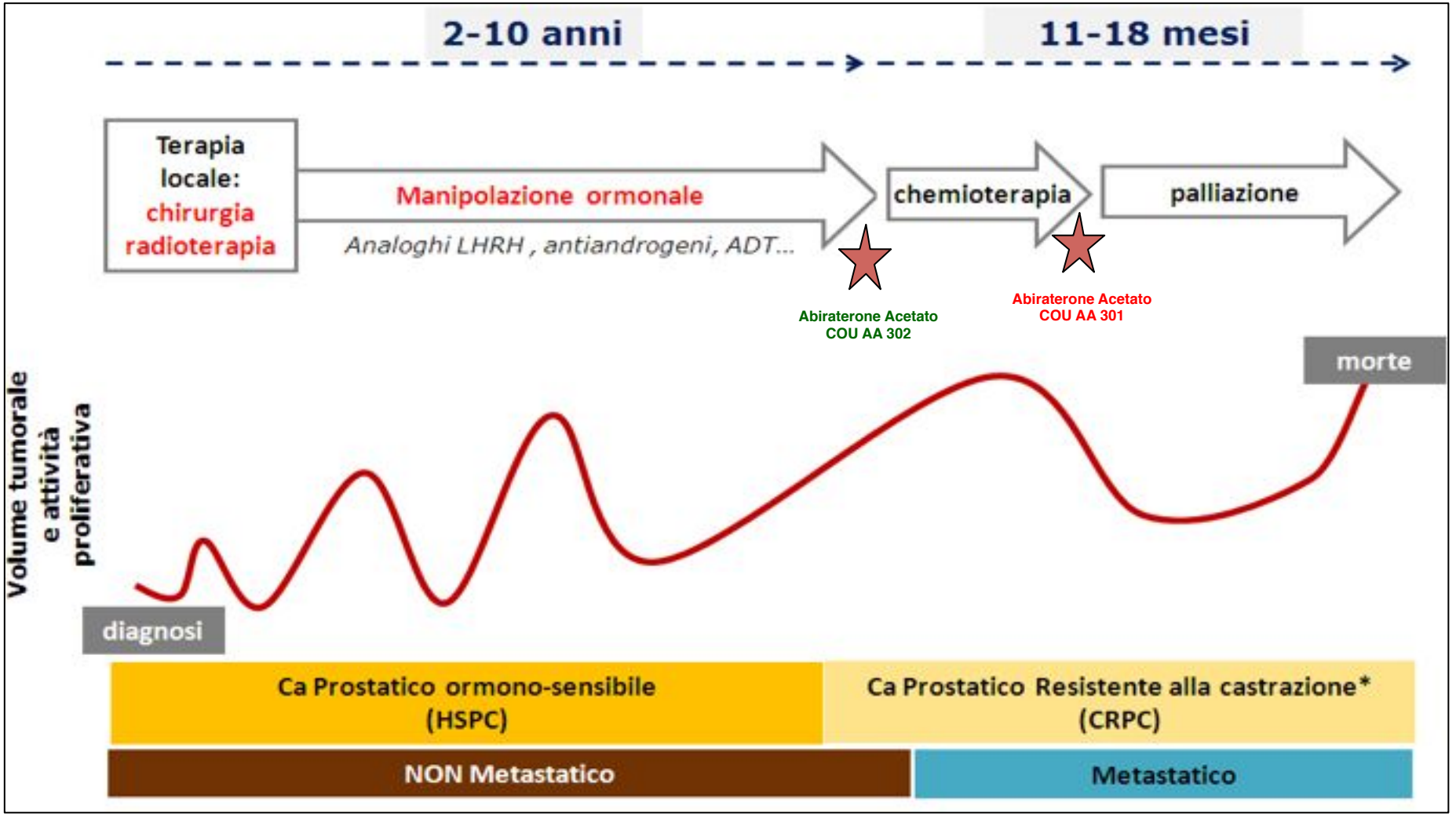
	Abiraterone acetate and prednisone (n=797)	Placebo and prednisone (n=398)
6 month event-free	82·2% (79·0–85·0)	72·1% (65·9–77·3)
12 month event-free	71·1% (66·8–74·9)	59·1% (51·4–66·1)
18 month event-free	63·6% (58·4–68·3)	57·2% (48·7–64·8)

Data are rate (95% CI).

Table 4: Skeletal-related events-free survival in the intention-to-treat population

Logothetis et al, *Lancet Oncol* 2012

ABIRATERONE COU-AA-302 study



Perché il "302"?

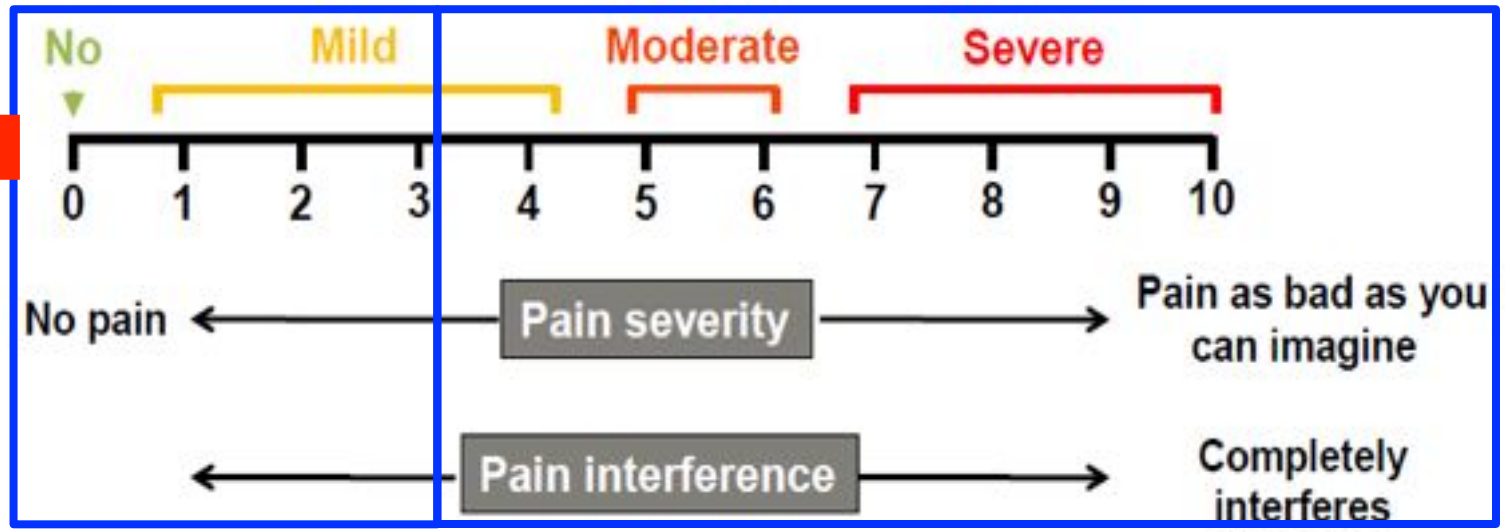
Per quale paziente?

Evaluation of pain: The Brief Pain Inventory

BPI-SF consists of 11 questions that assess:

- Pain severity at its 'worst', 'least', 'average' and 'now'
- Pain interference with daily functions

Patients rate pain severity and interference using an 11-point numerical rating scale



C H T

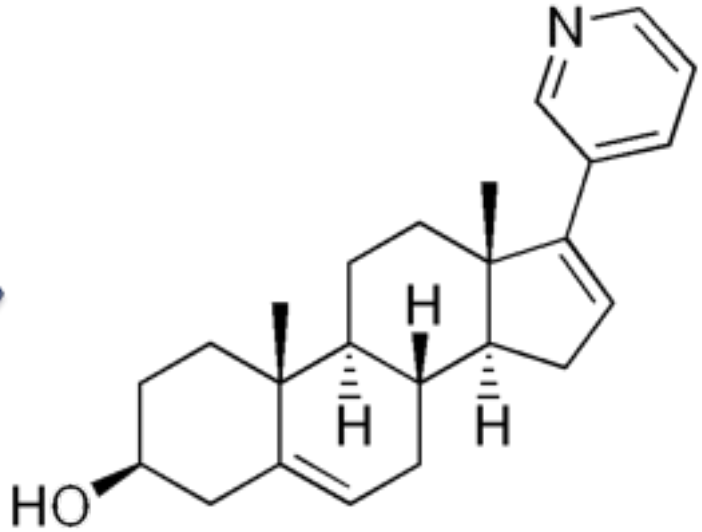
Cleeland CS. Clin Cancer Res 2006;12:6236–41; Cleeland CS. The Brief Pain Inventory: User Guide

PAZIENTE CRPC ASINTOMATICO O PAUCISINTOMATICO

Fino ad oggi erano possibili due scelte terapeutiche.

Tuttavia…nessuna di queste ha delle «evidenze di vantaggio»

Prolungare la terapia ormonale



Abiraterone Acetato

Anticipare la CHT

Eur Urol. 2014 Feb;65(2):467-79. doi: 10.1016/j.eururo.2013.11.002. Epub 2013 Nov 12.

EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer.

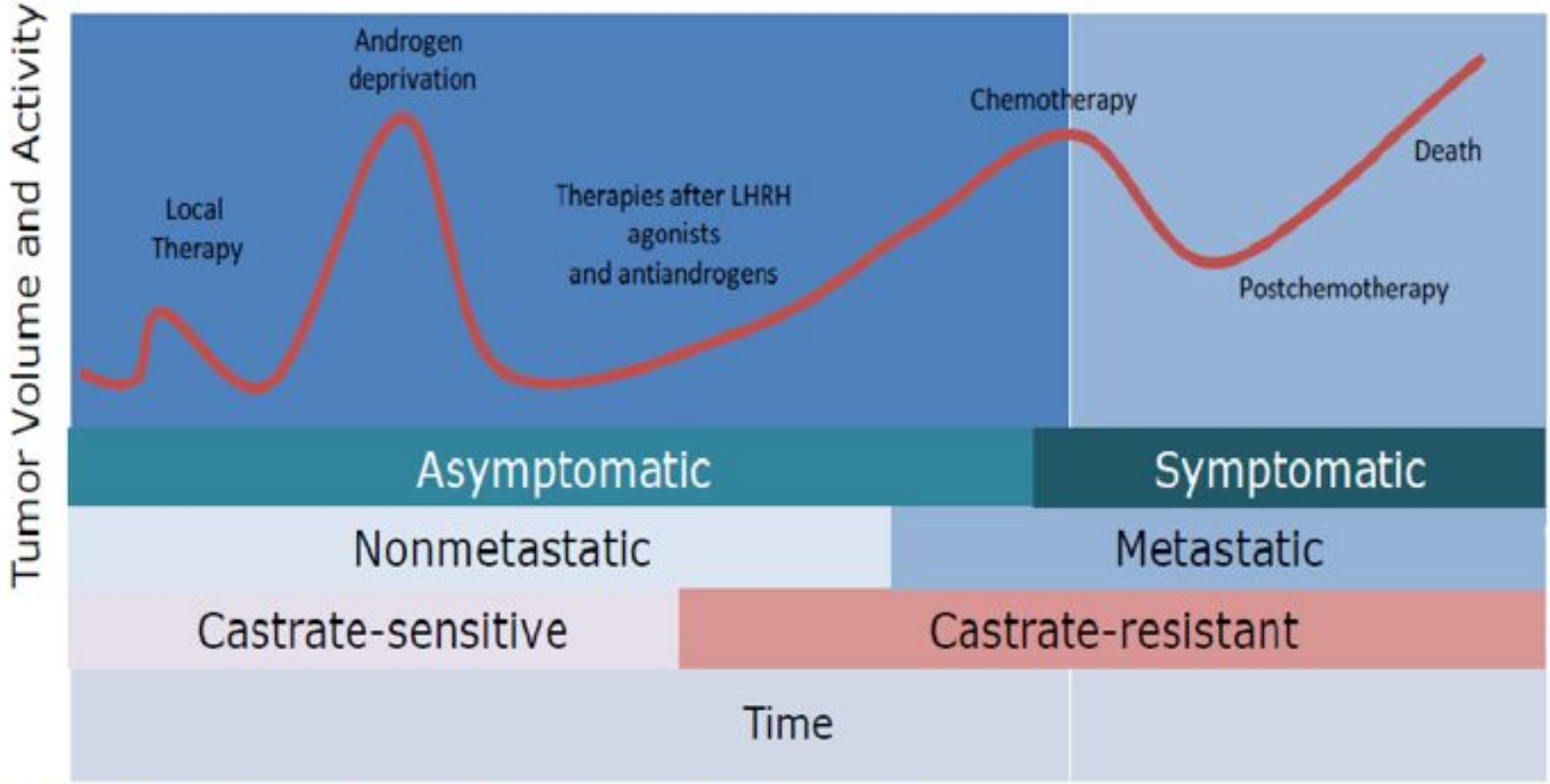
Heidenreich A[1], Bastian PJ[2], Bellmunt J[3], Bolla M[4], Joniau S[5], van der Kwast T[6], Mason M[7], Matveev V[8], Wiegel T[9], Zattoni F[10], Mottet N[11]; European Association of Urology.

Although many second-line treatment regimes have resulted in prolonged PFS and PSA responses, none of the approaches have resulted in an improved OS or CSS.

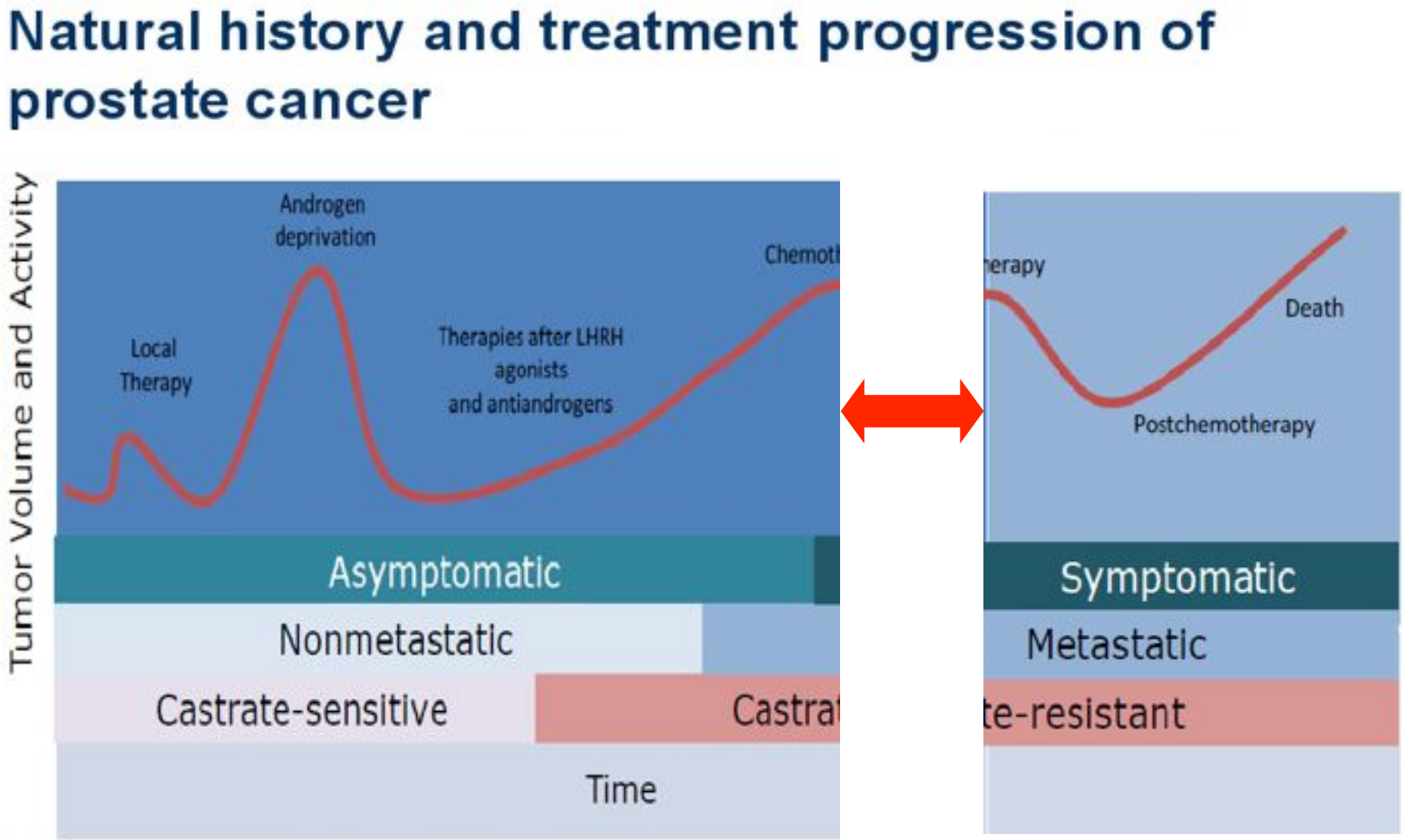
With the new hormonal and cytotoxic agents available, the use of unspecific second-line hormonal manipulations is no longer supported, necessary, or mandatory prior to the applications of the new substances.

"Why 302? From this….."

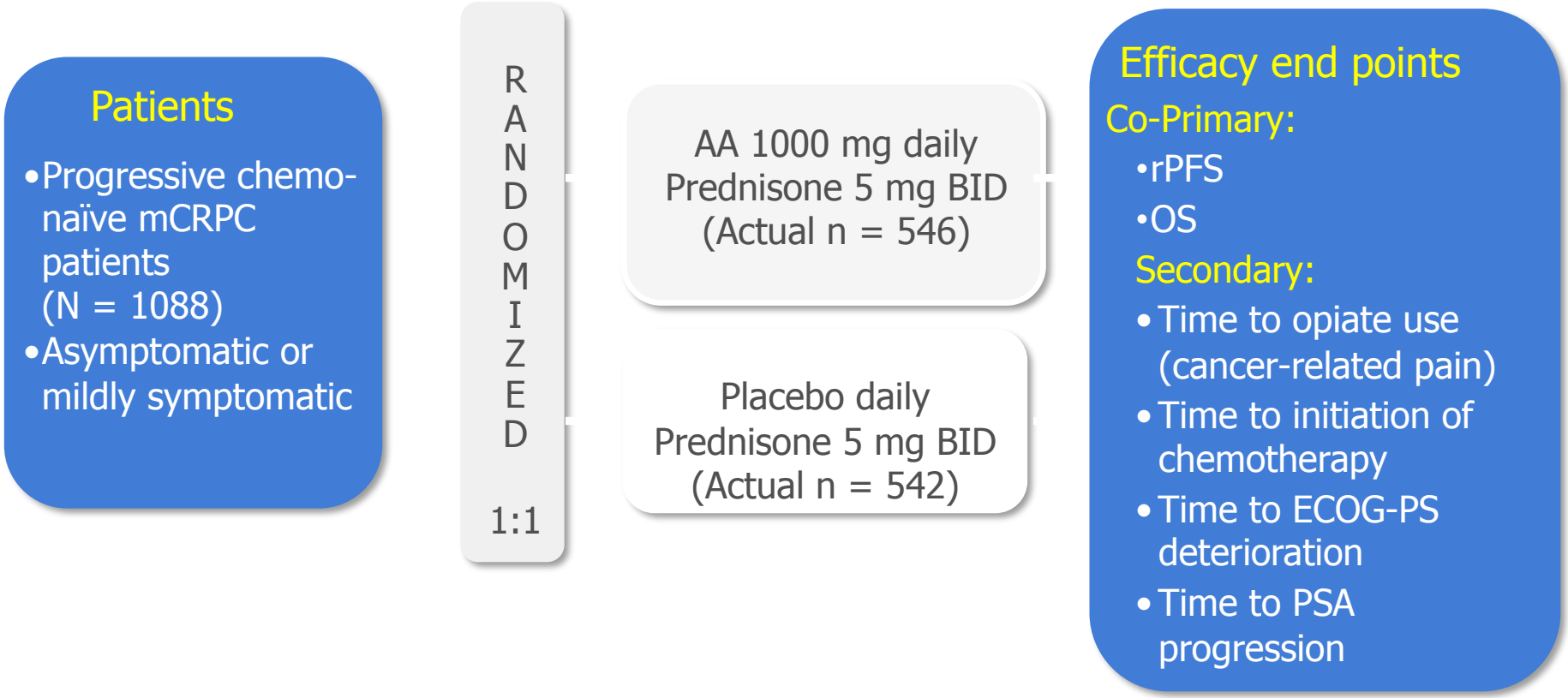
Natural history and treatment progression of prostate cancer



"….to this!"


Natural history and treatment progression of prostate cancer
Tumor Volume and Activity
Androgen deprivation
Local Therapy
Therapies after LHRH agonists and antiandrogers
Asymptomatic
Nonmetastatic
Castrate-sensitive
Time
Death
Postchemotherapy
Symptomatic
Metastatic

Overall Study Design of COU-AA-302



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 et al. N Engl J Med 2013

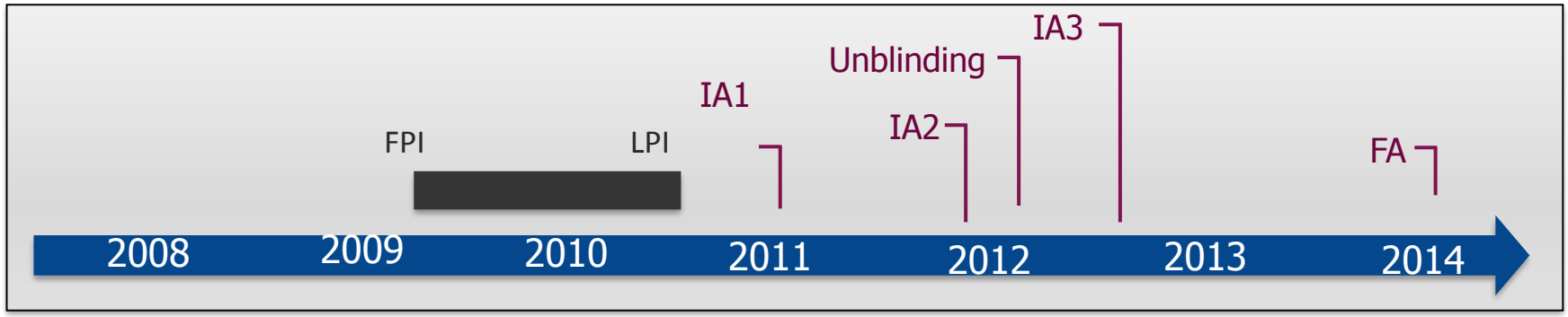
Treatment Arms Were Well Balanced at Baseline

	Abiraterone (n = 546)	Prednisone (n = 542)
Median age, years (range)	71 (44-95)	70 (44-90)
Median time from initial diagnosis to first dose (years)	5.5	5.1
Median PSA (ng/mL)	42.0	37.7
Gleason score (≥ 8) at initial diagnosis	54%	50%
Extent of disease		
Bone metastases	83%	80%
> 10 bone metastases	49%	47%
Soft tissue[a]	49%	50%
Pain (BPI-SF)		
0-1	66%	64%
2-3	32%	33%

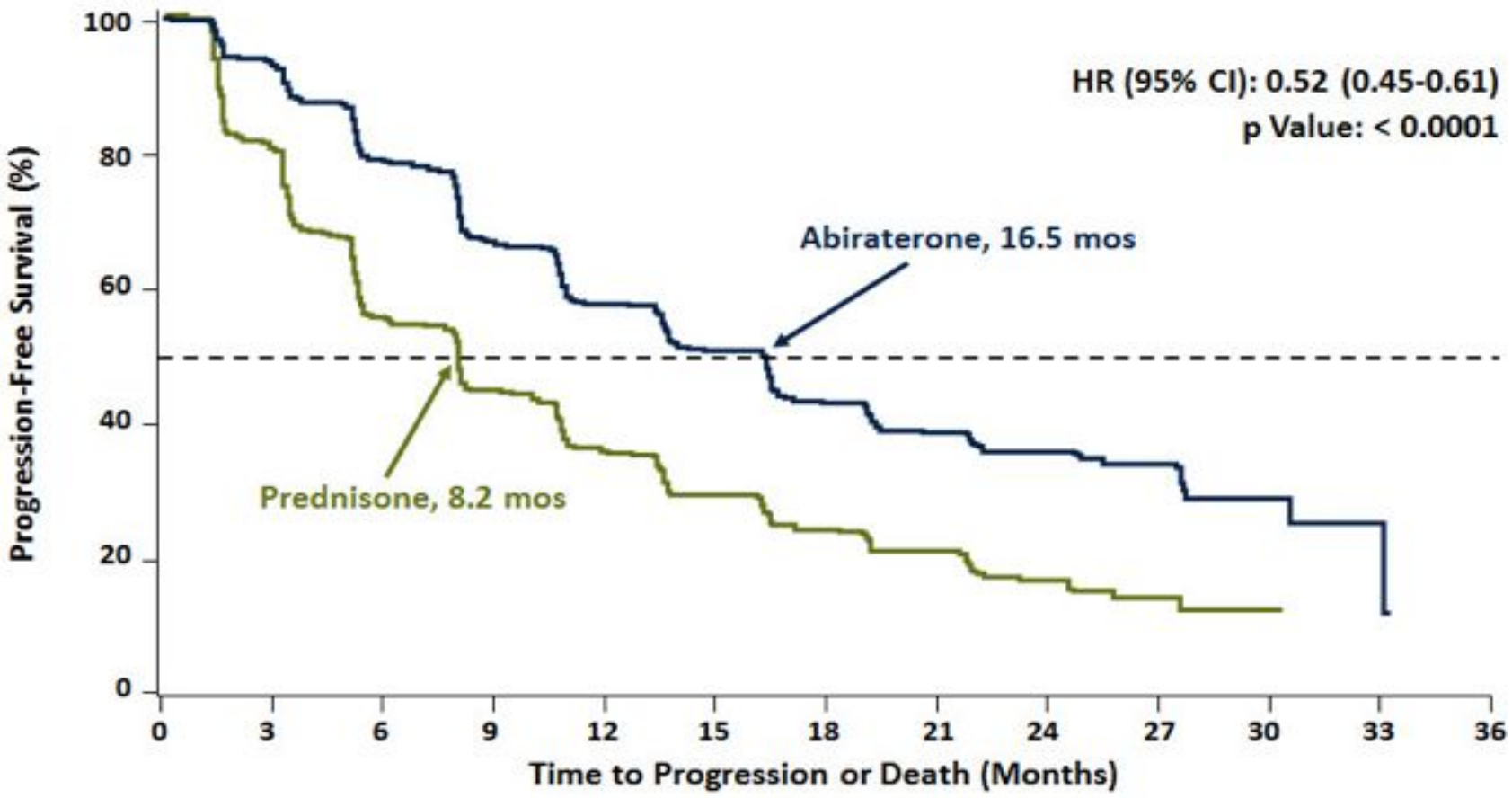
[a]Excludes visceral metastases.

COU-AA-302: Study Design

- February 2012
  - Investigators and sponsors remained blinded
  - Concluded that OS, rPFS, and secondary end points all favored AA
  - Recommended unblinding study and that patients in placebo arm be offered treatment with AA



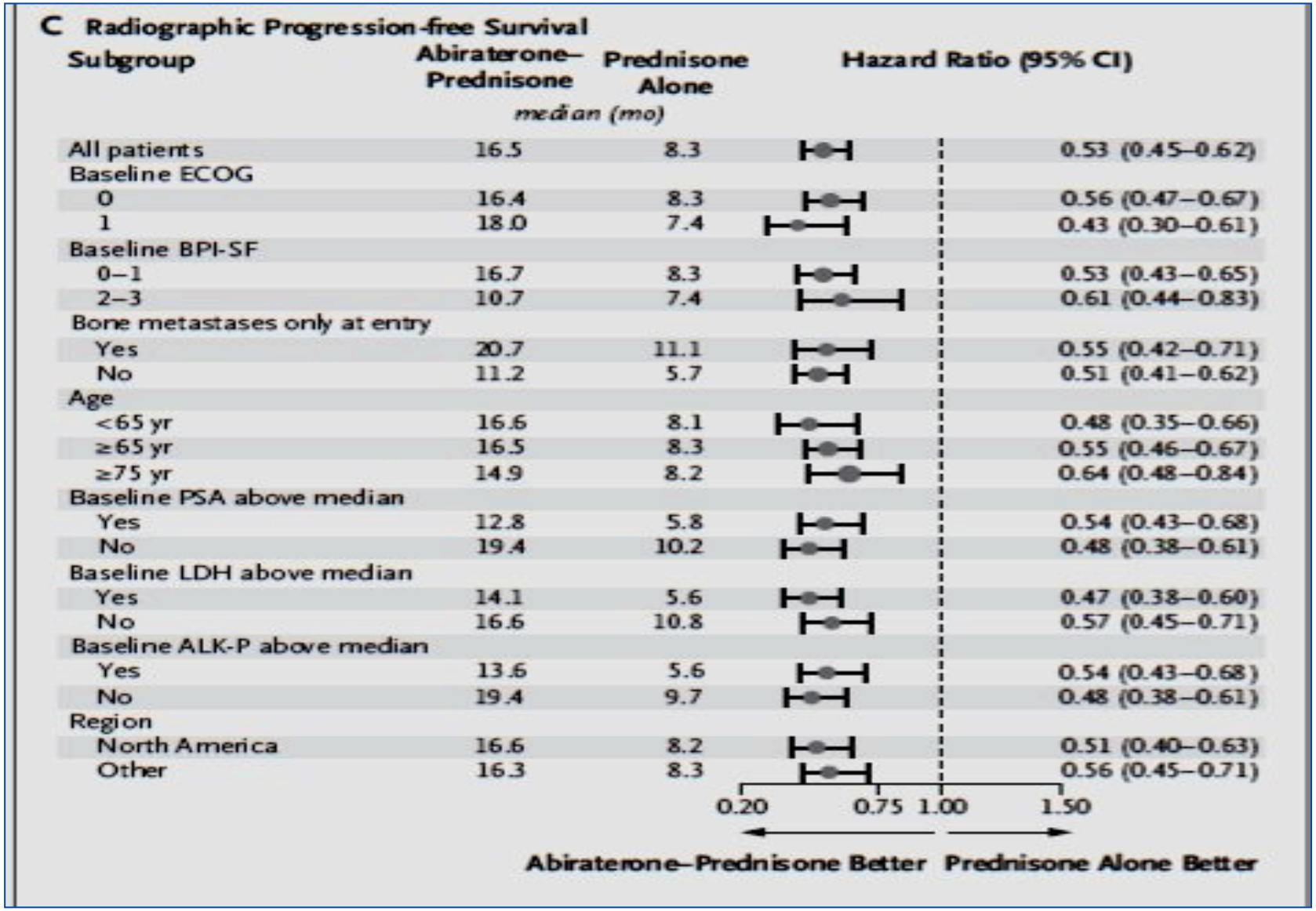
ABIRATERONE COU-AA-302 study



Abiraterone Doubled Time to rPFS

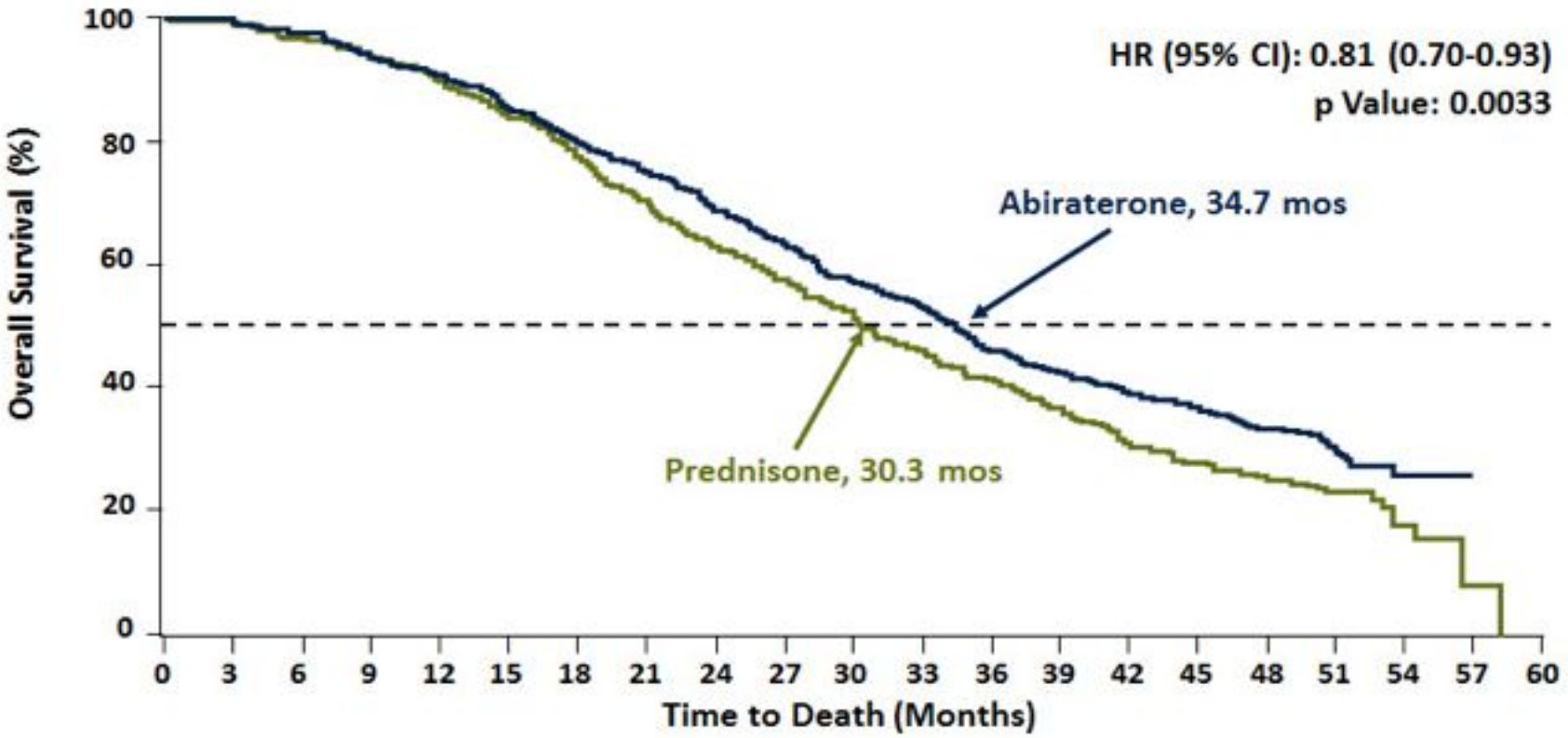
Rathkopf DE et al. *Eur Urol* 2014; Ryan C et al. ESMO 2014

ABIRATERONE COU-AA-302 study



Ryan, N Engl J Med 2013

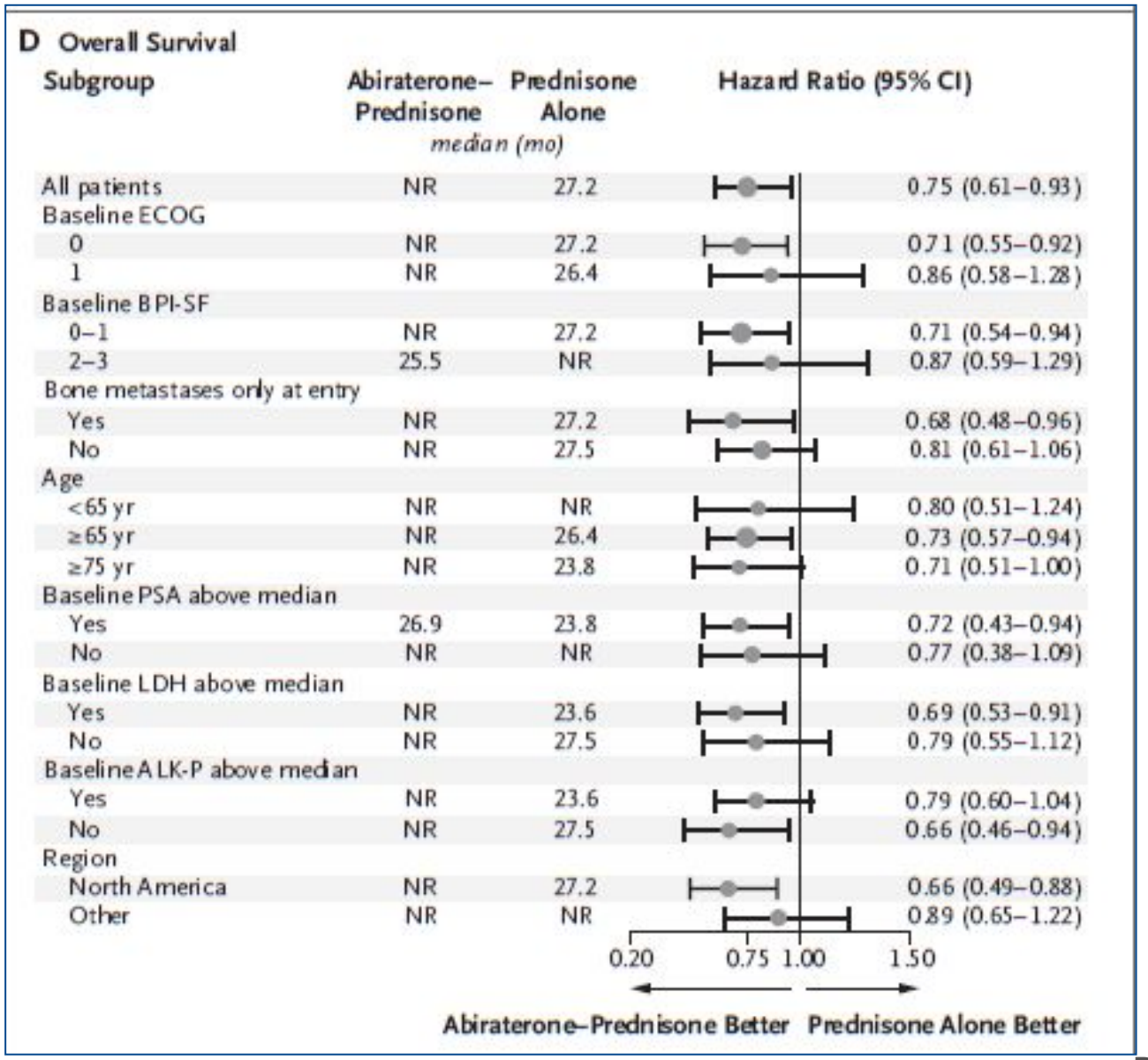
COU-AA-302: OS final analysis



Median follow-up of 49.2 months.
Abiraterone treatment effect more pronounced when adjusting for 44% of prednisone patients who received subsequent abiraterone (HR = 0.74) .

Ryan C et al. ESMO 2014;

ABIRATERONE COU-AA-302 study



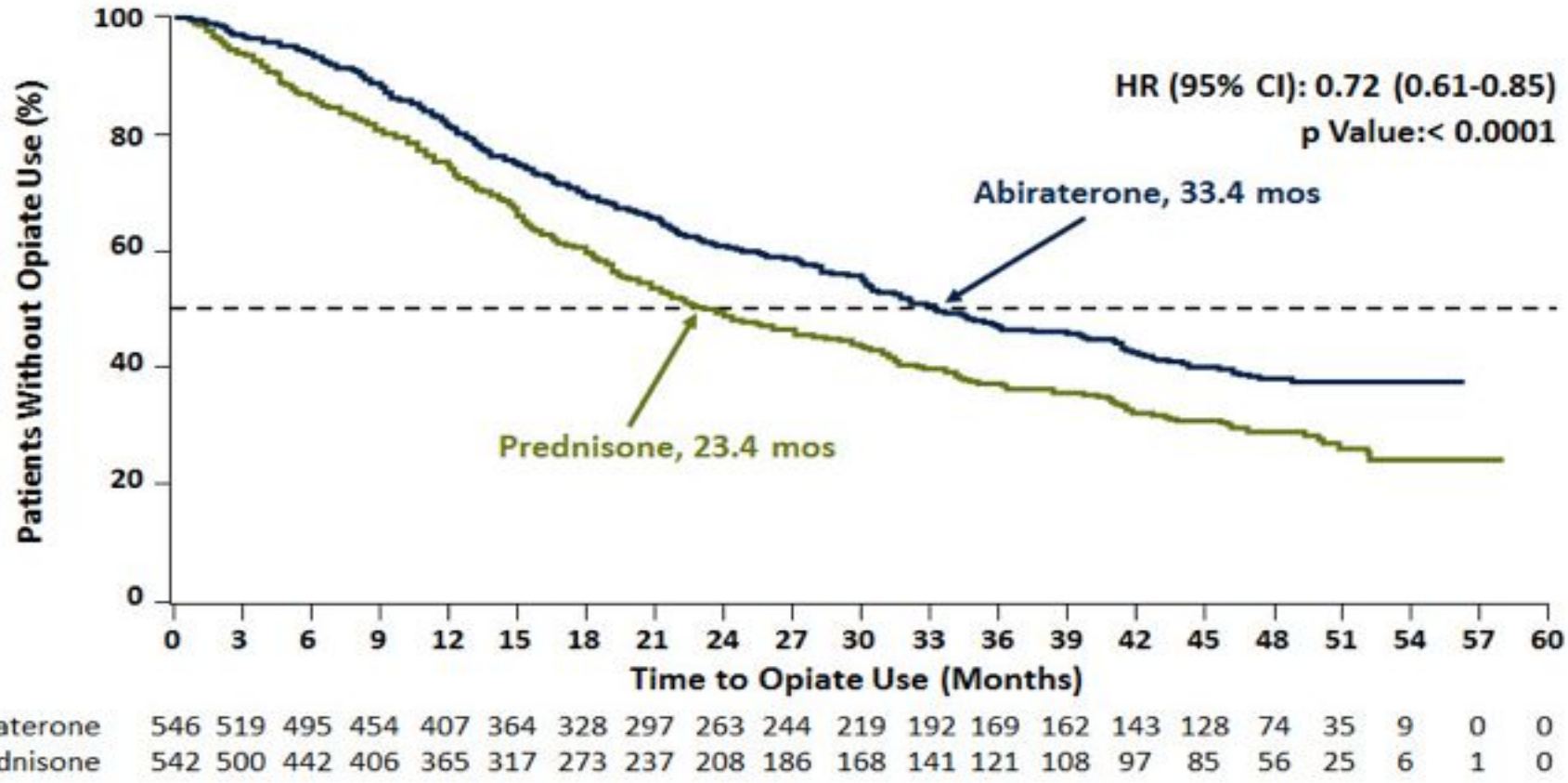
Ryan, N Engl J Med 2013

ABIRATERONE COU-AA-302 study

End Point	Abiraterone–Prednisone (N=546)	Prednisone Alone (N=542)	Value (95% CI)†	P Value
Secondary end points				
Median time to opiate use for cancer-related pain — mo	NR	23.7	0.69 (0.57–0.83)	<0.001
Median time to initiation of cytotoxic chemotherapy — mo	25.2	16.8	0.58 (0.49–0.69)	<0.001
Median time to decline in ECOG performance score by ≥1 point — mo	12.3	10.9	0.82 (0.71–0.94)	0.005
Median time to PSA progression — mo‡	11.1	5.6	0.49 (0.42–0.57)	<0.001
Exploratory end points§				
Median time to increase in pain — mo¶	26.7	18.4	0.82 (0.67–1.00)	0.049
Median time to functional-status decline measured as FACT-P total score — mo‖	12.7	8.3	0.78 (0.66–0.92)	0.003
Patients with decline of ≥50% in PSA level — %**	62	24	2.59 (2.19–3.05)††	<0.001
Patients with a RECIST response — %‡‡				
Defined objective response	36	16	2.27 (1.59–3.25)††	<0.001
Stable disease	61	69		
Progressive disease	2	15		

Ryan, N Engl J Med 2013

ABIRATERONE COU-AA-302 study



ESMO 2014: Significant Improvement in Time to Opiate Use for Cancer-Related Pain in the Final Analysis.

Ryan C et al. ESMO 2014;

ABIRATERONE COU-AA-302 study

Table 2. Adverse Events.*

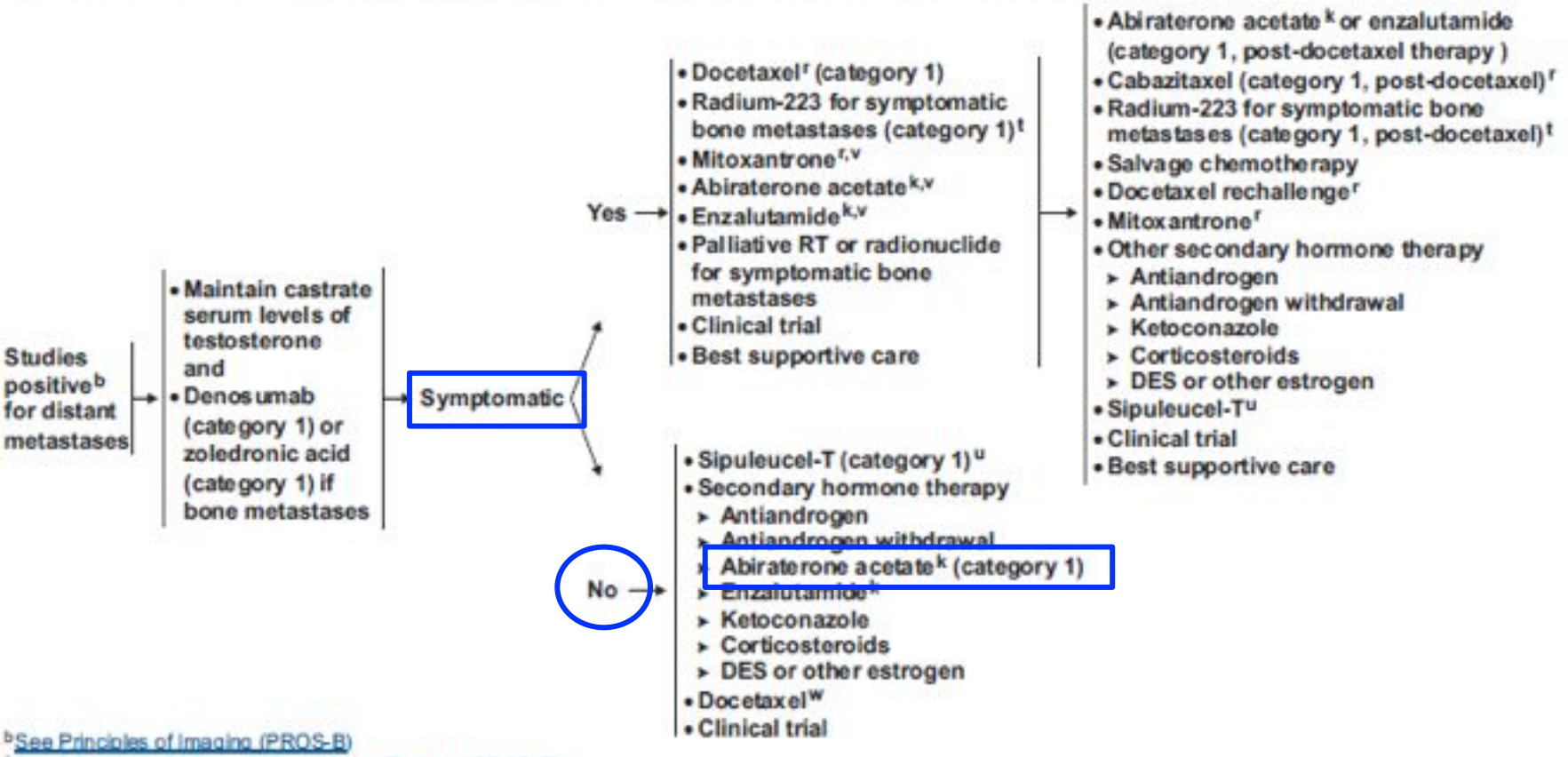
Adverse Event	Abiraterone–Prednisone (N=542)	Prednisone Alone (N=540)
	no. of patients (%)	
Any adverse event	537 (99)	524 (97)
Grade 3 or 4 adverse event	258 (48)	225 (42)
Any serious adverse event	178 (33)	142 (26)
Adverse event leading to treatment discontinuation	55 (10)	49 (9)
Adverse event leading to death*	20 (4)	12 (2)
Adverse event of grade 1–4 in ≥15% of patients in either group		
Fatigue	212 (39)	185 (34)
Back pain	173 (32)	173 (32)
Arthralgia	154 (28)	129 (24)
Nausea	120 (22)	118 (22)
Constipation	125 (23)	103 (19)
Hot flush	121 (22)	98 (18)
Diarrhea	117 (22)	96 (18)
Bone pain	106 (20)	103 (19)
Muscle spasm	75 (14)	110 (20)
Pain in extremity	90 (17)	85 (16)
Cough	94 (17)	73 (14)

Table 3. Adverse Events of Special Interest.*

Adverse Event	Abiraterone–Prednisone (N=542)		Prednisone Alone (N=540)	
	Grade 1–4	Grade 3 or 4	Grade 1–4	Grade 3 or 4
Fluid retention or edema	150 (28)	4 (<1)	127 (24)	9 (2)
Hypokalemia	91 (17)	13 (2)	68 (13)	10 (2)
Hypertension	118 (22)	21 (4)	71 (13)	16 (3)
Cardiac disorder†	102 (19)	31 (6)	84 (16)	18 (3)
Atrial fibrillation	22 (4)	7 (1)	26 (5)	5 (<1)
ALT increased	63 (12)	29 (5)	27 (5)	4 (<1)
AST increased	58 (11)	16 (3)	26 (5)	5 (<1)

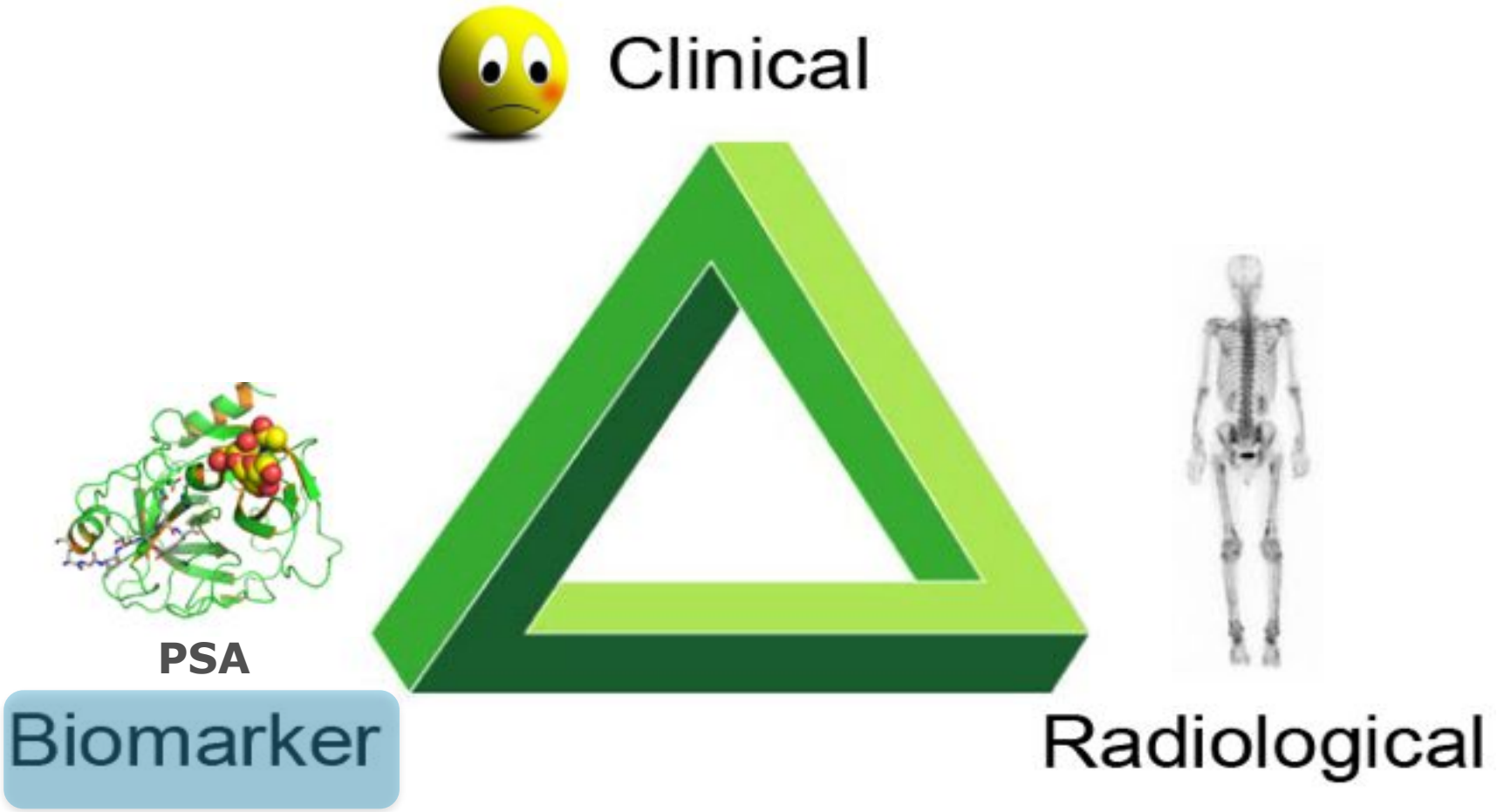
Ryan et al. N Engl J Med 2013

ADVANCED DISEASE: ADDITIONAL SYSTEMIC THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER



[b] See Principles of Imaging (PROS-B)
[k] See Principles of Androgen Deprivation Therapy (PROS-F).
[r] See Principles of Immunotherapy and Chemotherapy (PROS-G).
[t] Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D, page 2 of 2).
[u] Sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG performance status 0-1. Sipuleucel-T is not indicated in patients with hepatic metastases or life expectancy <6 months.
[v] For patients who are not candidates for docetaxel-based regimens.
[w] Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or hepatic metastases despite lack of symptoms.

CRPC: Focus sulla progressione



Criteria for Progression/Discontinuation of Study Therapy

Within the COU-AA-301 study, to confirm progression and therefore discontinue study treatment, **all three of the following criteria were required**:

1. PSA progression as defined by PSAWG eligibility criteria (25% increase over baseline) with minimum PSA increase of 5 ng/mL.

2. Radiographic progression defined by at least one of the following:

- Progression on bone scans with ≥ 2 new lesions not consistent with tumor flare, confirmed on a second bone scan ≥ 6 weeks later that shows ≥1 additional new lesion.
- Soft tissue disease progression by modified RECIST criteria (baseline LN size must be ≥ 2.0 cm to be considered target or evaluable lesion).

3. Symptomatic or clinical progression defined by one of the following:

- Pain progression - Worsening of pain due to metastatic bone disease defined as an increase of ≥ 30% in the worst pain over the past 24 hours on the Brief Pain Inventory- Short Form (BPI-SF) numeric rating scale observed at 2 consecutive evaluations 4 weeks apart without decrease in analgesic usage score, or an increase in analgesic usage score ≥ 30% observed at 2 consecutive evaluations 4 weeks apart; to qualify as progression, the patient must have a BPI-SF score ≥ 4
- Development of a Skeletal Related Event (SRE) defined as pathologic fracture, spinal cord compression, palliative radiation to bone, or surgery to bone
- Any increase in prednisone or prednisolone dose or a change to a more potent glucocorticoid such as dexamethasone, to treat prostate cancer related signs and symptoms, such as fatigue and pain is considered a disease progression event
- Treating physician decides to initiate new systemic anti-cancer therapy

PSA Flare in Prostate Cancer

PSA flare: A transient rise in PSA, after initiation of a treament.

- Median time to flare 3 weeks and median duration 12 weeks
- Up to 20% of prostate cancer patients
- Seen with many treatments

Early increase in PSA within the first 12 weeks should be ignored, in absence of other signs of clinical progression.

ASCO | Annual '12 Meeting

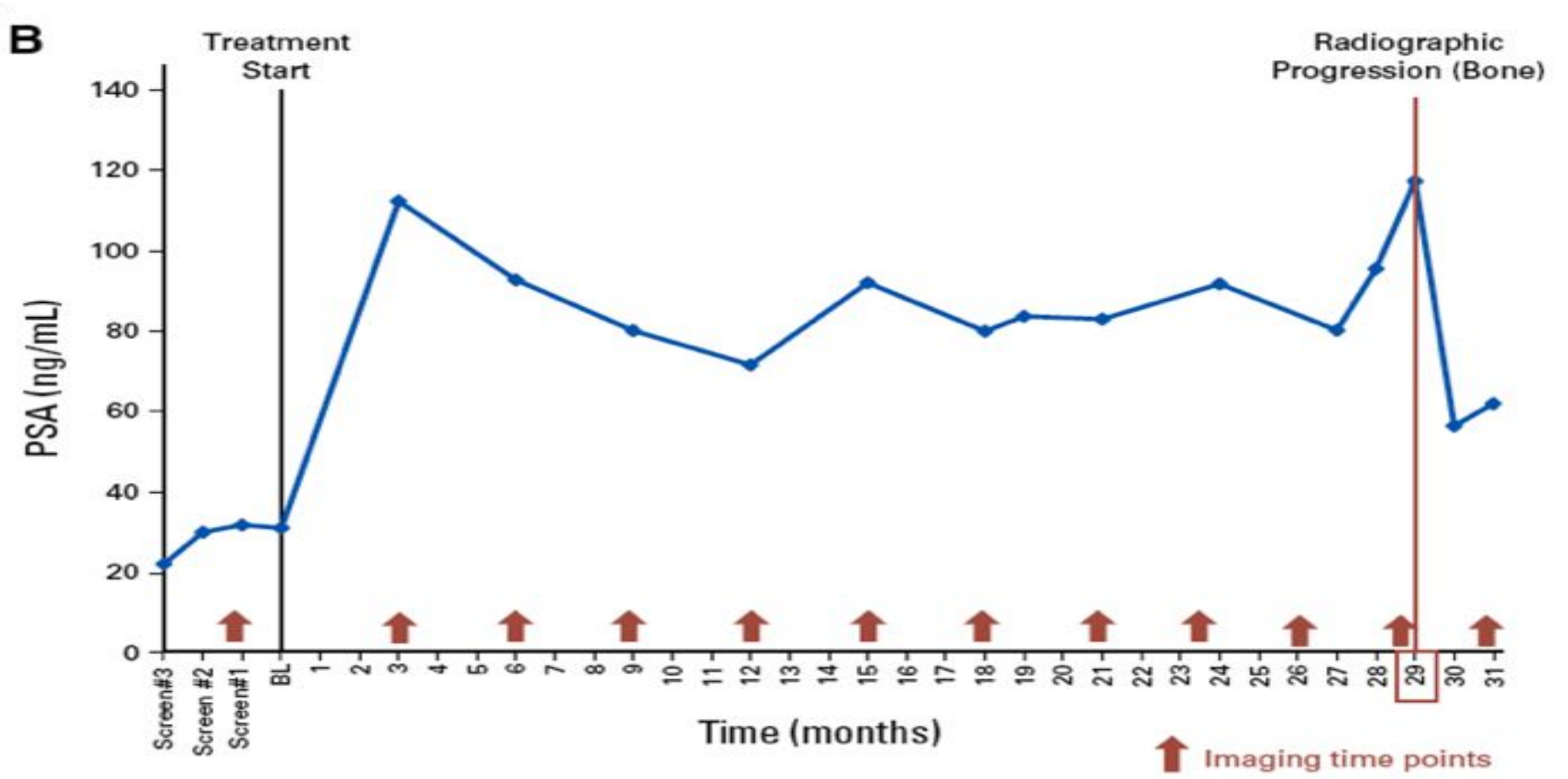
June 1-5, 2012 | McCormick Place | Chicago, Illinois

Durable radiologic and clinical disease stability beyond PSA progression in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with abiraterone acetate (AA).

Background: AA, a potent oral CYP17A1 inhibitor is approved for treatment of mCRPC with a survival advantage of 4.9 months. In clinical practice, response evaluation remains challenging for pts with mCRPC. CTC conversion from CTC ≥ 5 to CTC < 5 with treatment predicts for improved overall survival in mCRPC. We hypothesized that pts continue to have durable disease stability beyond PSA progression on AA. **Methods:** Prostate Specific Antigen (PSA) responses, radiological responses and CTC conversion rates were retrospectively analysed in pts treated on AA at our institution. CTCs, PSA and imaging were obtained at predefined time points during these studies. Radiological and PSA progression were defined by standard Prostate Cancer Working Group Criteria II. Clinical progression consisted of worsening disease related pain, skeletal events or declining performance status.Pearson's chi-squared test and the Kaplan-Meier method were used for this analysis. **Results:** 141 patients [ECOG Performance Status 0-2; Median Age: 69.7 (range 44.7-87.1); 85 post-docetaxel, 56 pre-docetaxel] received AA. The median duration of clinical and radiological stable disease (SD) was 16.8 months (n=55) and 5.6 months (n=75) in patients with a baseline CTCs count of ≤ 5 cells/7.5mls and ≥ 5 cells/7.5 mls respectively. In the 105 patients with documented PSA progression on AA there was a median 5.7-month delay in detecting radiological and/or clinical progression (95% CI: 4.2, 8.4; range 0.3, 35.6 months). Radiological and clinical SD of ≥ 1 year, ≥ 2 years and ≥ 3 years on AA was observed in 43/141 (30.5%), 21/141 (14.9%) and 12/141 (8.5%) respectively. **Conclusions:** Radiological and clinical disease stabilization beyond PSA progression is maintained in a high proportion of mCRPC patients treated with AA. Future studies should evaluate whether continued AA treatment beyond PSA and radiological progression can impact outcome.

"....In 105 (out of 141 patients) with documented PSA progression on AA, there was a median 5.7-month delay in detecting radiological and/or clinical progression....."

Bianchini D et al. J Clin Oncol 2012;
Bianchini D et al. Poster presentation, ASCO

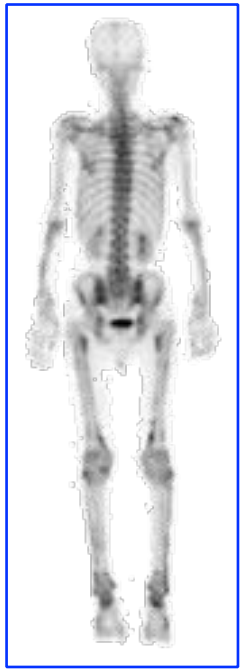


"...an initial rapid rise in PSA with subsequent decline above baseline on a second value in a patient who remained biochemically, radiographically, and clinically stable for 22 months on abiraterone."

Mod. da Scher et al., J Clin Oncol 29

The definition of progression

Clinical



Biomarker

Radiological

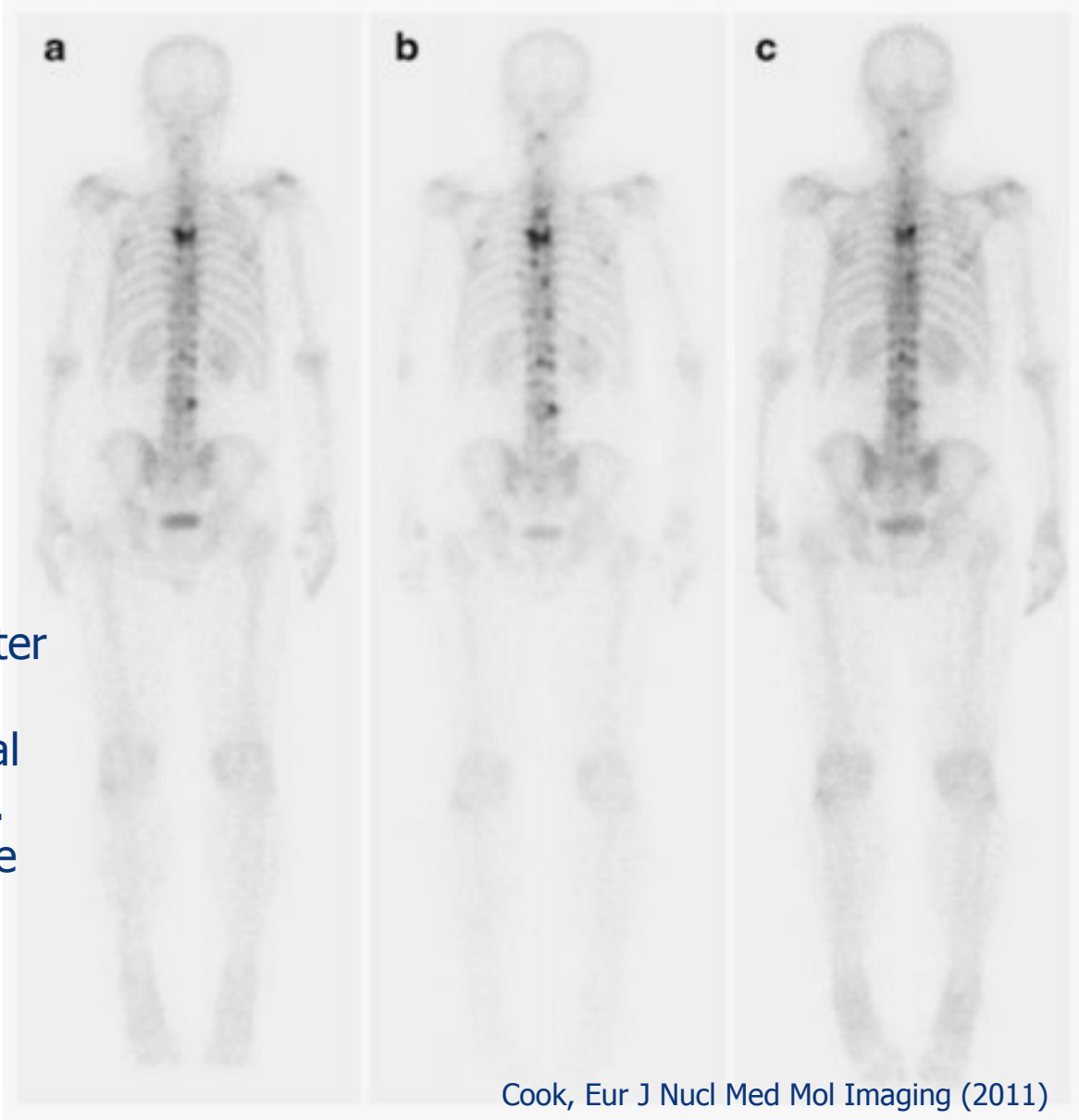
BONE FLARE PHENOMENON

The bone flare phenomenon describes an increase in isotope uptake by metastatic lesions or the appearance of new, previously occult lesions, soon after starting systemic hormone or chemotherapy, resulting from the osteoblastic healing response in a skeletal metastasis.

The flare phenomenon is reported to be greatest up to 3 months after commencing systemic therapy and has usually subsided by approximately 6 months.

It is also reported to occur in between 6 and 23% of patients with metastatic prostate cancer.

BONE FLARE PHENOMENON



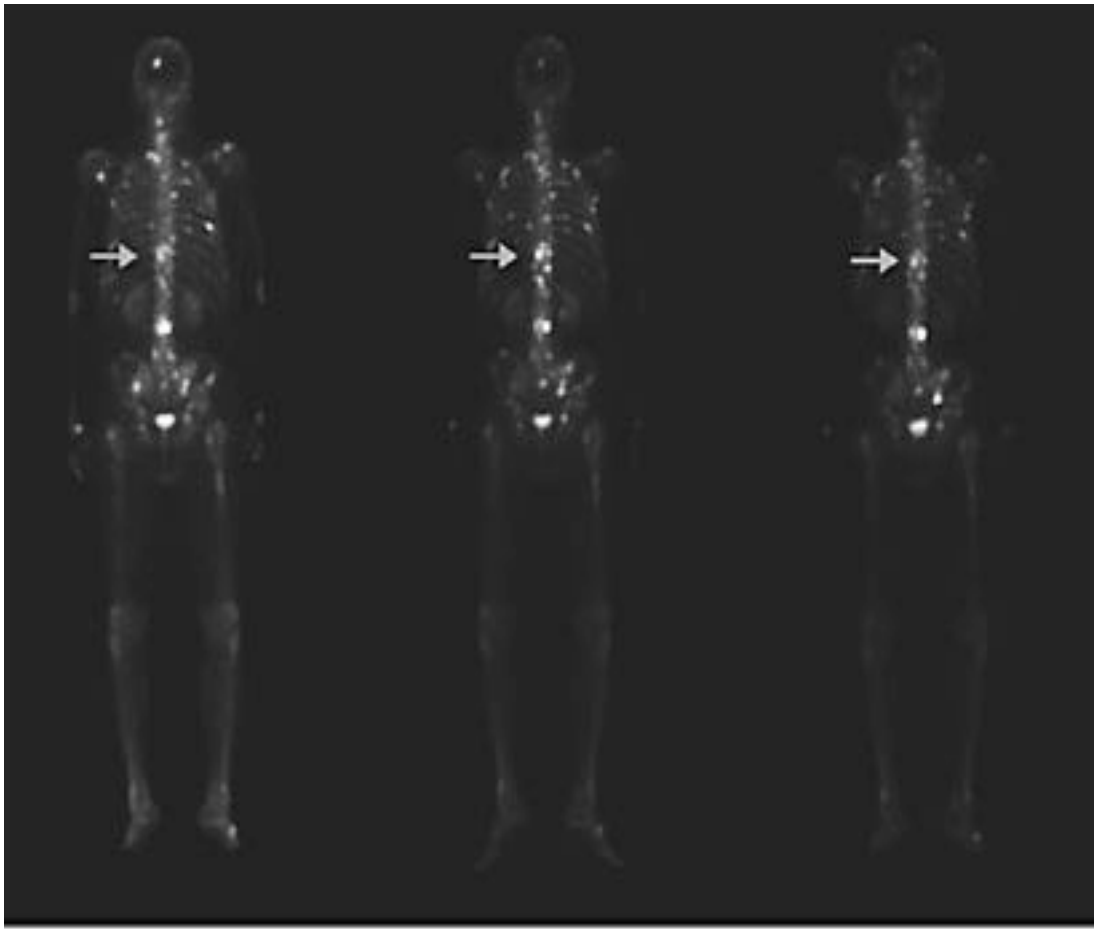
Bone scans at baseline (a), 6 weeks (b) and 6 months (c) after commencing first-line hormones. There is clear evidence of skeletal metastases on the baseline scan. The metastases show an increase in intensity at 6 weeks which subsequently reduces, typical of the flare phenomenon.

Cook, Eur J Nucl Med Mol Imaging (2011)

Phase II Study of Abiraterone Acetate in Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer Displaying Bone Flare Discordant with Serologic Response

Charles J. Ryan[1], Shreya Shah[1], Eleni Efstathiou[2], Matthew R. Smith[3], Mary-Ellen Taplin[4], Glenn J. Bubley[5], Christopher J. Logothetis[2], Thian Kheoh[6], Christine Kilian[1], Christopher M. Haqq[6], Arturo Molina[6], and Eric J. Small[1]

Bone flare phenomenon



Baseline
Multifocal
PSA 41.7

Month 4
Progression in existing lesions
PSA 4.52

Month 7
Stable/slight improvement
PSA 4.27

Examples of bone scan flare in patients receiving abiraterone acetate.

Patient with a declining PSA level but a month 4 bone scan being read as progression in existing lesions.
By month 7, this progression improved, indicating that the progression seen at month 4 was due to bone flare.

Ryan et al., Clin Cancer Res, 2011

Cancer Therapy: Clinical

Cancer Research

Phase II Study of Abiraterone Acetate in Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer Displaying Bone Flare Discordant with Serologic Response

Charles J. Ryan[1], Shreya Shah[1], Eleni Efstathiou[2], Matthew R. Smith[3], Mary-Ellen Taplin[4], Glenn J. Bubley[5], Christopher J. Logothetis[2], Thian Kheoh[6], Christine Kilian[1], Christopher M. Haqq[6], Arturo Molina[6], and Eric J. Small[1]

Abstract

Purpose: Abiraterone is an oral inhibitor of CYP17, which is essential for androgen biosynthesis. This multicenter study assessed its efficacy in patients with castration-resistant prostate cancer (CRPC), without prior chemotherapy or CYP17-targeted therapy, and frequency of bone scans discordant with prostate-specific antigen (PSA) and clinical response.

Experimental Design: Thirty-three patients received abiraterone acetate 1,000 mg daily with prednisone 5 mg twice daily in continuous 28-day cycles. Patients were evaluated monthly for efficacy and safety. Bone scan flare was defined as the combination, after 3 months of therapy, of an interpreting radiologist's report indicating "disease progression" in context of a 50% or more decline in PSA level, with scan improvement or stability 3 months later.

Results: A 50% or more decline in PSA level at week 12 was confirmed in 22 of 33 (67%) patients. Declines in PSA level of 50% or more were seen in 26 of 33 (79%) patients. Undetectable PSA levels ($\leq$0.1 ng/mL) occurred in 2 patients. Median time on therapy and time to PSA progression were 63 weeks and 16.3 months, respectively. Twenty-three patients were evaluable for bone scan flare. Progression was indicated in radiologist's report in 12 of 23 (52%), and 11 of 12 subsequently showed improvement or stability. As prospectively defined, bone scan flare was observed in 11 of 23 (48%) evaluable patients or 11 of 33 (33%) enrolled patients. Adverse events were typically grade 1/2 and consistent with prior published abiraterone reports.

Conclusion: Clinical responses to abiraterone plus prednisone were frequent and durable in men with metastatic CRPC. Further investigation is needed to clarify the confounding effect of bone scan flare on patient management and interpretation of results. *Clin Cancer Res; 17(14); 4854–61. ©2011 AACR.*

The flare phenomenon was a common event: 48% of responding patients

How do we define progression in the clinic?

Symptomatic or clinical progression defined by one of the following:

Pain progression: Worsening of pain due to metastatic bone disease defined as an increase of ≥ 30% in the worst pain over the past 24 hours on the BPI-SF numeric rating scale observed at 2 consecutive evaluations 4 weeks apart without decrease in analgesic usage score, or an increase in analgesic usage score ≥ 30% observed at 2 consecutive evaluations 4 weeks apart; to qualify as progression, the patient must have a BPI-SF score ≥ 4;

Development of a skeletal related event (SRE) defined as pathologic fracture, spinal cord compression, palliative radiation to bone, or surgery to bone;

Any increase in prednisone or prednisolone dose or a change to a more potent glucocorticoid such as dexamethasone, to treat prostate cancer related signs and symptoms, such as fatigue and pain is considered a disease progression event;

Treating physician decides to initiate new systemic anti-cancer therapy

Fonte: Clinical Study Protocol: COU-AA-301

Unequivocal clinical progression

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Use of Abiraterone Acetate in combination with Radiotherapy

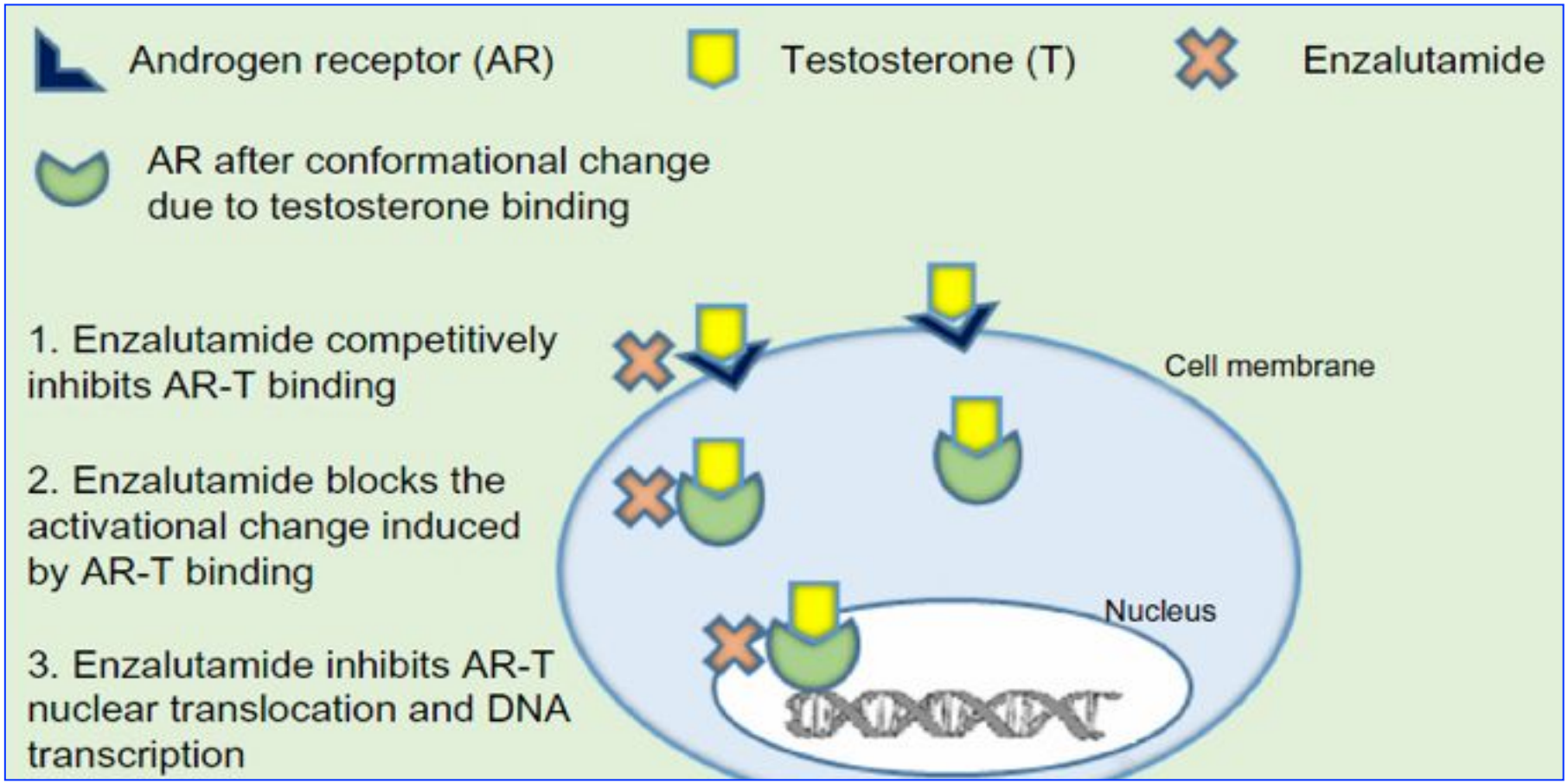
Use of Abiraterone Acetate in combination with Radiotherapy

- Within the COU-AA-301 study, the use of palliative radiation was permitted. The study allowed for one course of radiation (single or multi-fraction) to a single site.
- In the COU-AA-301 study, 11.1% of patients in the abiraterone arm and 12.2% in the placebo arm had localized progression at a single site and received concurrent palliative radiotherapy;
- No new safety signals were seen in patients receiving abiraterone plus prednisone and palliative radiation.

De Bono J et al.NEJM 2011;
Saad F et. 2012

Enzalutamide

Enzalutamide



Enzalutamide is an androgen-receptor–signaling inhibitor. Enzalutamide has 5-8 fold higher binding affinity to AR than the first generation anti-androgen bicalutamide.

Patel, Therapeutics and Clinical Risk Management. 2014

The NEW ENGLAND JOURNAL of MEDICINE

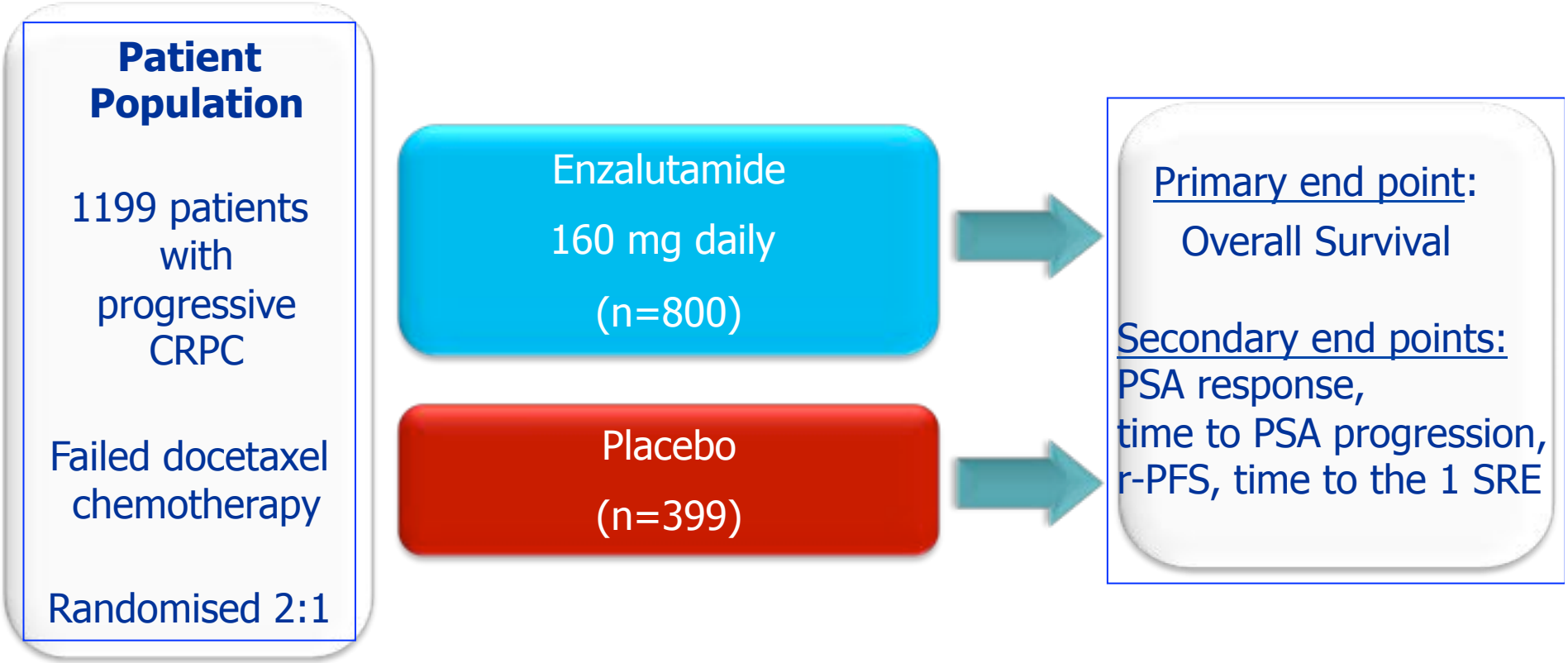
ESTABLISHED IN 1812 SEPTEMBER 27, 2012 VOL. 367 NO. 13

Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy

Howard I. Scher, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Mary-Ellen Taplin, M.D., Cora N. Sternberg, M.D., Kurt Miller, M.D., Ronald de Wit, M.D., Peter Mulders, M.D., Ph.D., Kim N. Chi, M.D., Neal D. Shore, M.D., Andrew J. Armstrong, M.D., Thomas W. Flaig, M.D., Aude Fléchon, M.D., Ph.D., Paul Mainwaring, M.D., Mark Fleming, M.D., John D. Hainsworth, M.D., Mohammad Hirmand, M.D., Bryan Selby, M.S., Lynn Seely, M.D., and Johann S. de Bono, M.B., Ch.B., Ph.D., for the AFFIRM Investigators*

The AFFIRM (A Study Evaluating the Efficacy and Safety of the Investigational Drug ENZALUTAMIDE).

AFFIRM Phase III Trial of ENZALUTAMIDE in Post-Chemotherapy treated mCRPC



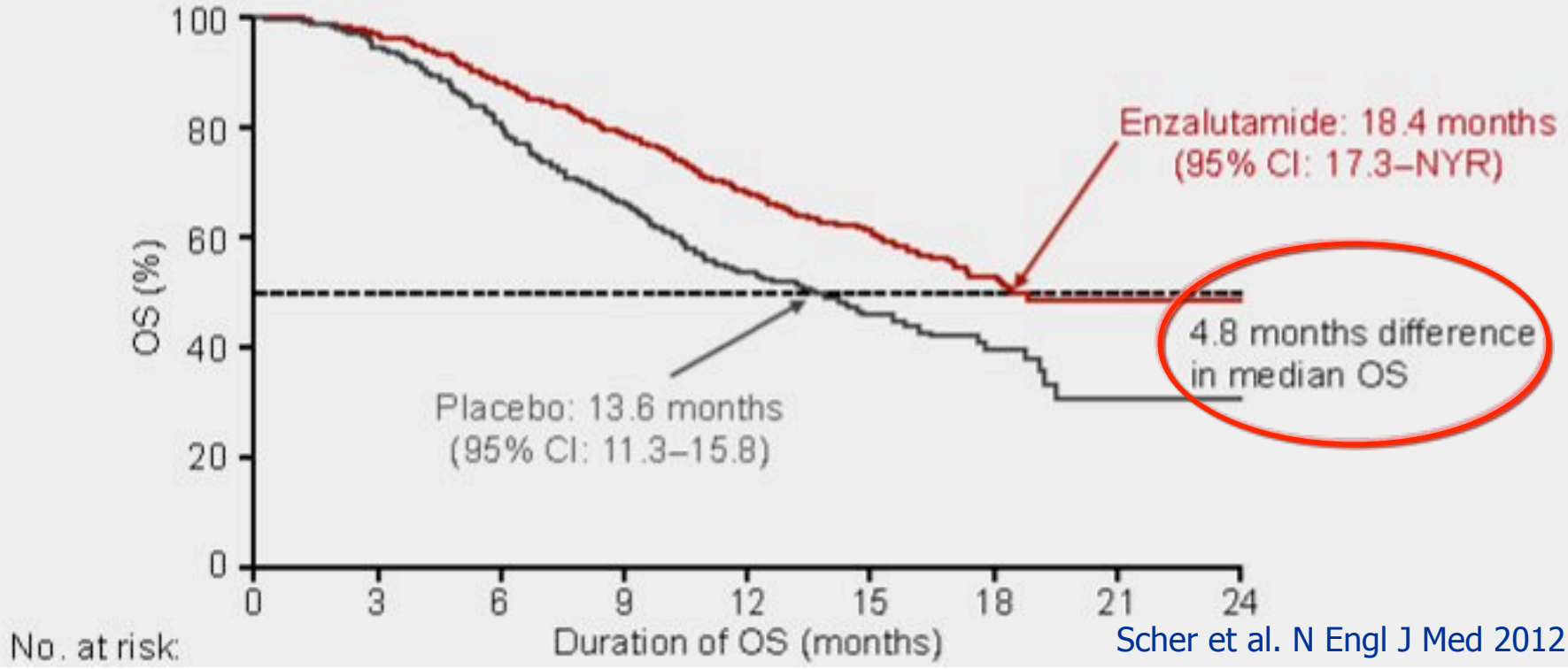
* Glucocorticoids were not required but allowed.

Scher et al. N Engl J Med 2012

AFFIRM Phase III Trial of ENZALUTAMIDE in Post-Chemotherapy treated mCRPC

OS (primary endpoint)

- Enzalutamide significantly improved OS compared with placebo:
  - Median OS was 18.4 versus 13.6 months, respectively (p<0.001)
  - 37% reduction in the risk of death (HR=0.63, CI: 0.53–0.75; p<0.001)

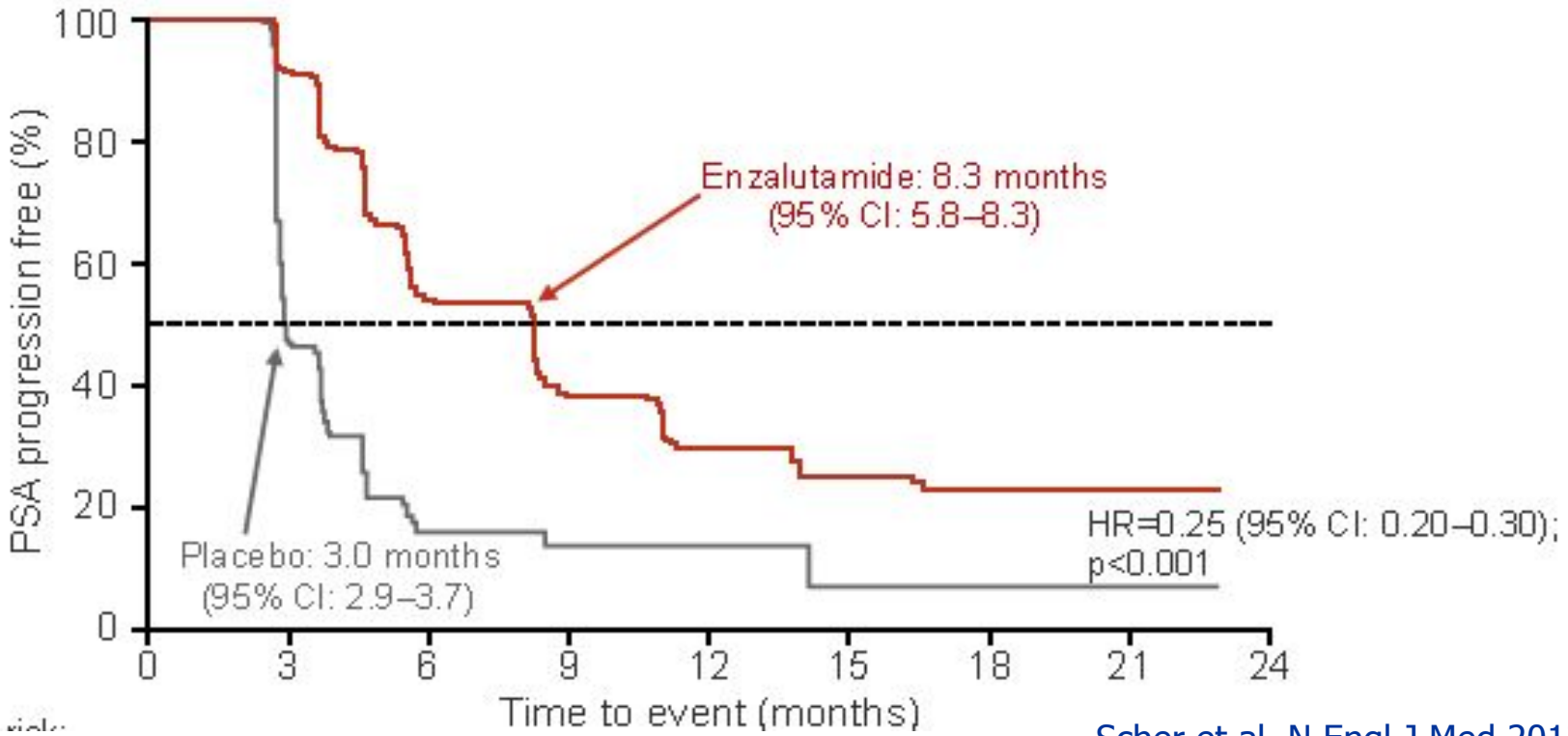


Scher et al. N Engl J Med 2012

AFFIRM Phase III Trial of ENZALUTAMIDE in Post-Chemotherapy treated mCRPC

Time to PSA progression (secondary endpoint)

- Time to PSA progression* was significantly longer with enzalutamide compared with placebo (8.3 vs. 3.0 months, respectively (p<0.001)



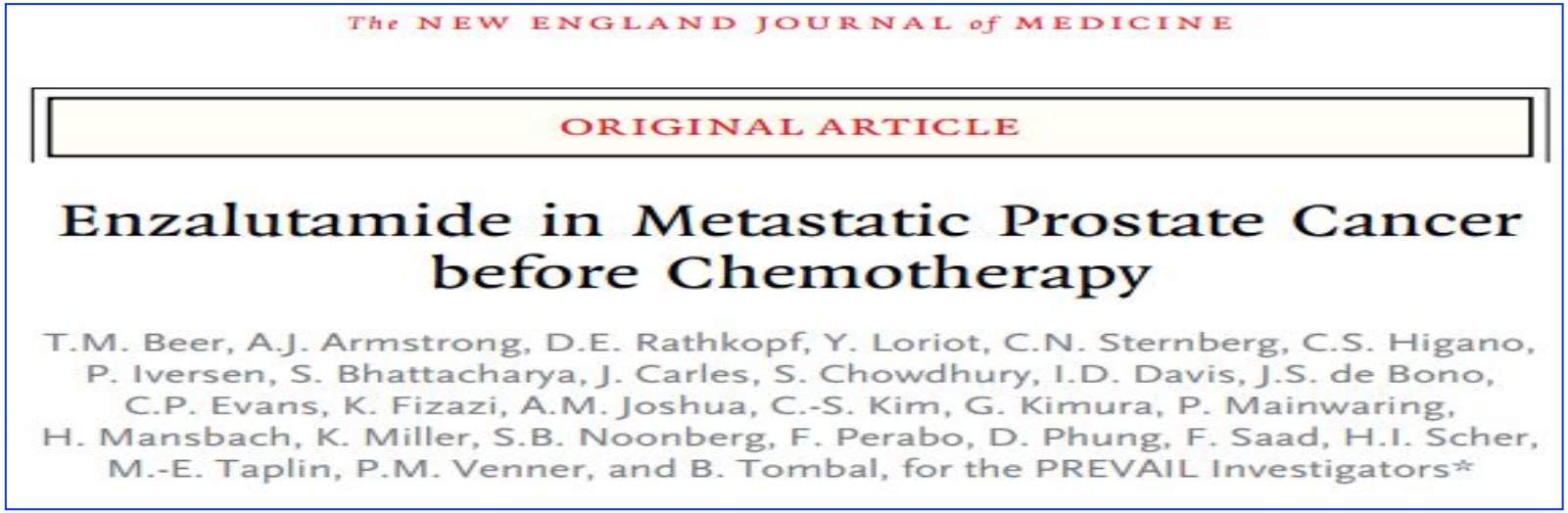
Scher et al. N Engl J Med 2012

AFFIRM Phase III Trial of ENZALUTAMIDE in Post-Chemotherapy treated mCRPC

Table 3. Adverse Events, According to Grade.

Adverse Event	Enzalutamide (N=800)		Placebo (N=399)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
≥1 Adverse event	785 (98)	362 (45)	390 (98)	212 (53)
Any serious adverse event	268 (34)	227 (28)	154 (39)	134 (34)
Discontinuation owing to adverse event	61 (8)	37 (5)	39 (10)	28 (7)
Adverse event leading to death	23 (3)	23 (3)	14 (4)	14 (4)
Frequent adverse events more common with enzalutamide*				
Fatigue	269 (34)	50 (6)	116 (29)	29 (7)
Diarrhea	171 (21)	9 (1)	70 (18)	1 (<1)
Hot flash	162 (20)	0	41 (10)	0
Musculoskeletal pain	109 (14)	8 (1)	40 (10)	1 (<1)
Headache	93 (12)	6 (<1)	22 (6)	0
Clinically significant adverse events				
Cardiac disorder				
Any	49 (6)	7 (1)	30 (8)	8 (2)
Myocardial infarction	2 (<1)	2 (<1)	2 (<1)	2 (<1)
Abnormality on liver-function testing†	8 (1)	3 (<1)	6 (2)	3 (<1)
Seizure	5 (<1)	5 (<1)	0	0

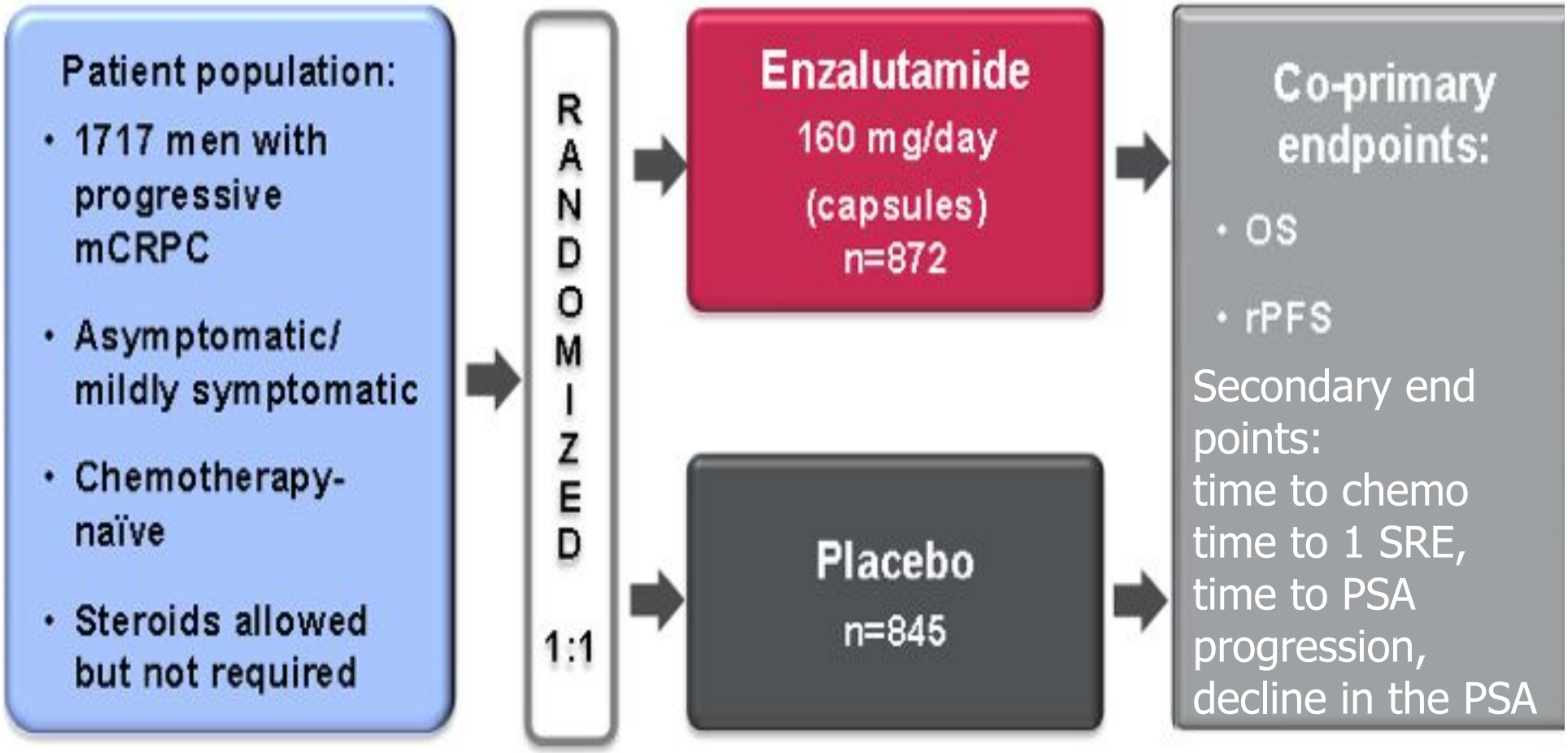
Scher et al. N Engl J Med 2012



Enzalutamide in Men with Chemotherapy-Naïve mCRPC Results of the Phase 3 PREVAIL Study

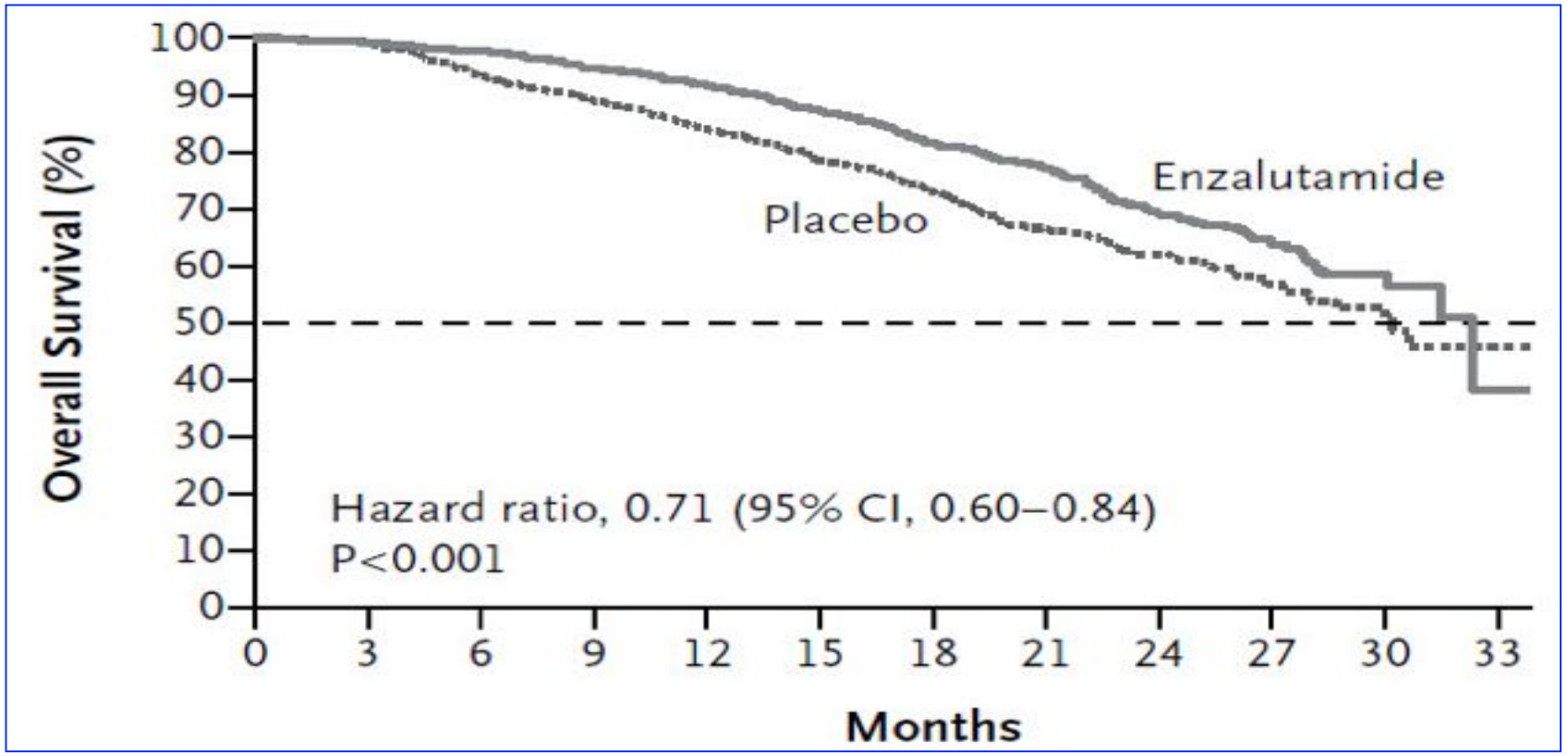
Beer T et al. N Engl J Med 2014;

PREVAIL Phase III Trial of ENZALUTAMIDE after progression on ADT in mCRPC



Beer T et al. N Engl J Med 2014;

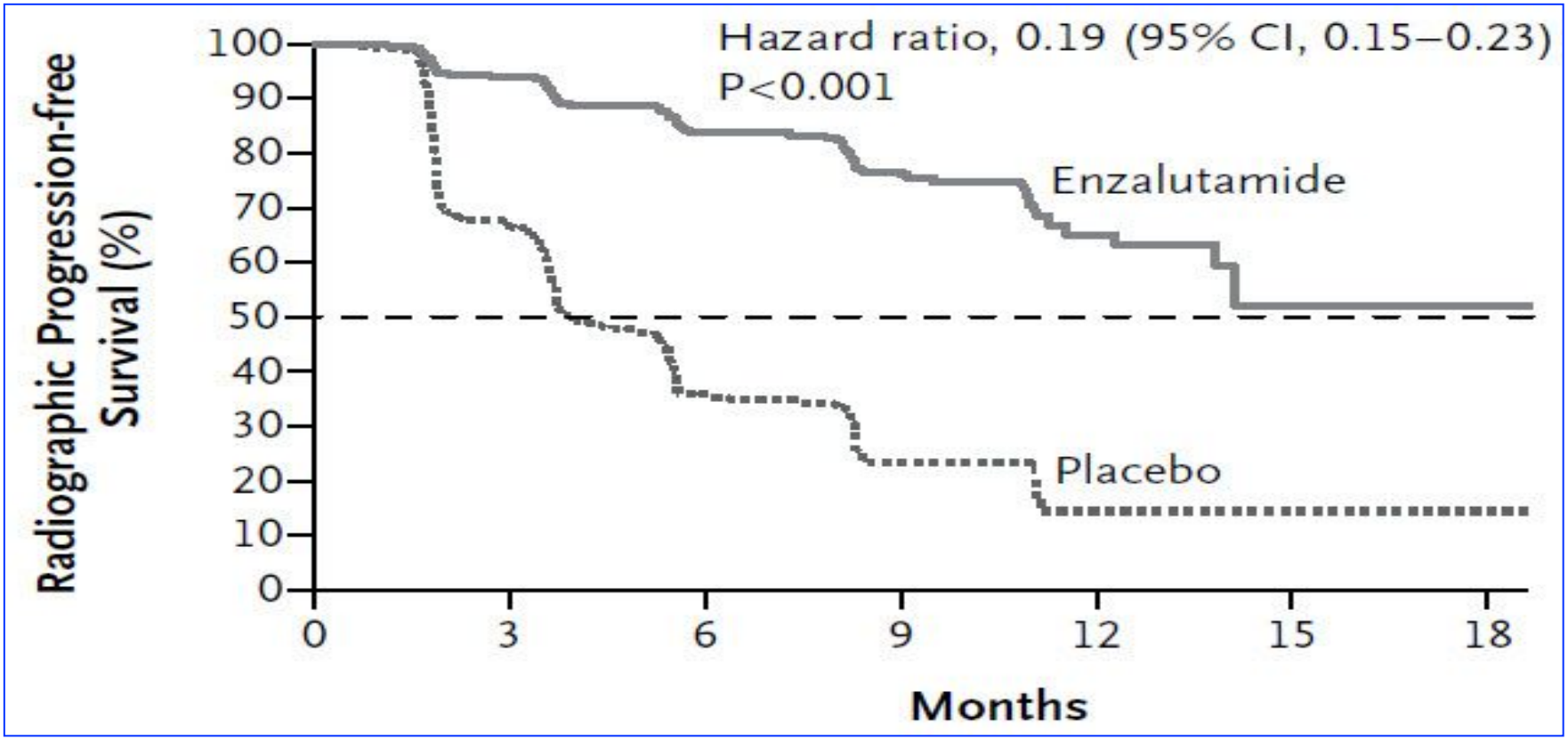
PREVAIL Phase III Trial of ENZALUTAMIDE after progression on ADT in mCRPC



Enzalutamide Reduced Risk of Death by 29%.
Median OS for Enzalutamide was 32.4 months vs. 30.2 months in the placebo group.

Beer T et al. N Engl J Med 2014;

PREVAIL Phase III Trial of ENZALUTAMIDE after progression on ADT in mCRPC



At 12 months of FUP, rPFS was 65% in the Enzalutamide group vs. 14% in the placebo group.
Enzalutamide Reduced Risk of rPFS by 81%.

Beer T et al. N Engl J Med 2014;

TABLE 3. Current Clinical Investigations in Sequential and Combination Therapies for Advanced Prostate Cancer

Sequencing studies

Chemotherapy-naive mCRPC

NCT01981122: Concurrent vs sequential treatment with **sipuleucel-T** and **enzalutamide** in mCRPC

Chemotherapy-naive or postchemotherapy mCRPC

NCT01487863: Concurrent vs sequential treatment with **sipuleucel-T** and **abiraterone** in men with mCRPC

Combination studies

AR therapies

Chemotherapy-naive mCRPC

NCT01949337: A phase 3 study of **enzalutamide** with or without **abiraterone** in patients with mCRPC

Chemotherapy-naive or postchemotherapy mCRPC

NCT01792687: A phase 1 study of **ARN-509** in combination with **abiraterone** in mCRPC

AR and non-AR therapies

Chemotherapy-naive mCRPC

NCT01565928: A phase 1 study of enzalutamide and docetaxel in men with advanced prostate cancer

NCT01685125: Abiraterone acetate with or without **dasatinib** in treating patients with mCRPC

NCT01995058: A study of **cabozantinib** in combination with **abiraterone** in patients with bone-metastatic CRPC

NCT01553188: A phase 2 study of **AMG386** and **abiraterone** in patients with mCRPC

NCT02106507: ARN509 plus **everolimus** in men with progressive metastatic castration-resistant prostate cancer after treatment with abiraterone acetate

Chemotherapy-naive or postchemotherapy mCRPC

NCT01685268: A phase 1/2 study of **HSP90 inhibitor AT13387** alone or in combination with **abiraterone**

NCT01576172: A phase 2 study of **abiraterone** with or without **veliparib** in treating patients with mCRPC

NCT01741753: BKM120 and **abiraterone** for patients with mCRPC

Postchemotherapy mCRPC

NCT01972217: A phase 2 study of **olaparib** with **abiraterone** in treating mCRPC

NCT01848067: A phase 1/2 study of **alisertib** in combination with **abiraterone** and prednisone for patients with CRPC after progression on abiraterone

NCT01511536: Cabazitaxel and **abiraterone** in patients with mCRPC

NCT01885949: Tivozanib and **enzalutamide** in advanced prostate cancer

Abbreviations: AR, androgen receptor; CRPC, castration-resistant prostate cancer; HSP90, heat-shock protein 90; mCRPC, metastatic castration-resistant prostate cancer; NCT, National Clinical Trials identifier.

What is the optimal sequence?

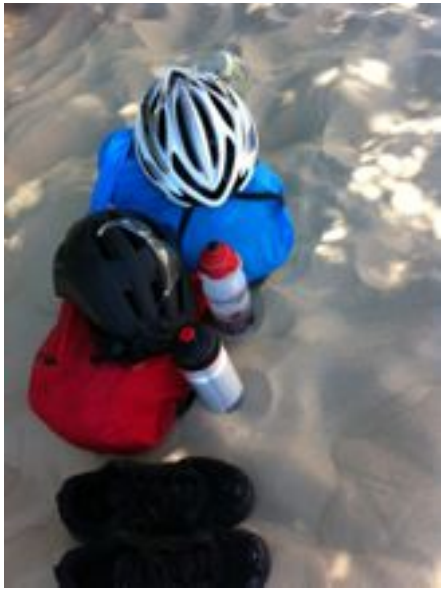
I am tired of the question…..no data!

- Reasonable to use less toxic therapies first
- Reasonable to involve patients in the decision making and respect patient preferences

I believe….patients should have exposure to as many active drugs as possible

- So long as the patient tolerates the drug well and does not "rapidly" progress, keep it going
- Do not let the patient deteriorate too far, that limits future options….follow patients closely

From Oliver Sartor ASCO 2012 Educational Session



Grazie per l' attenzione