IL CARCINOMA PROSTATICO:NUOVE ACQUISIZIONI E IMPLICAZIONI CLINICHE

L’INNOVAZIONE NELLA TERAPIA DELLA FASE METASTATICA

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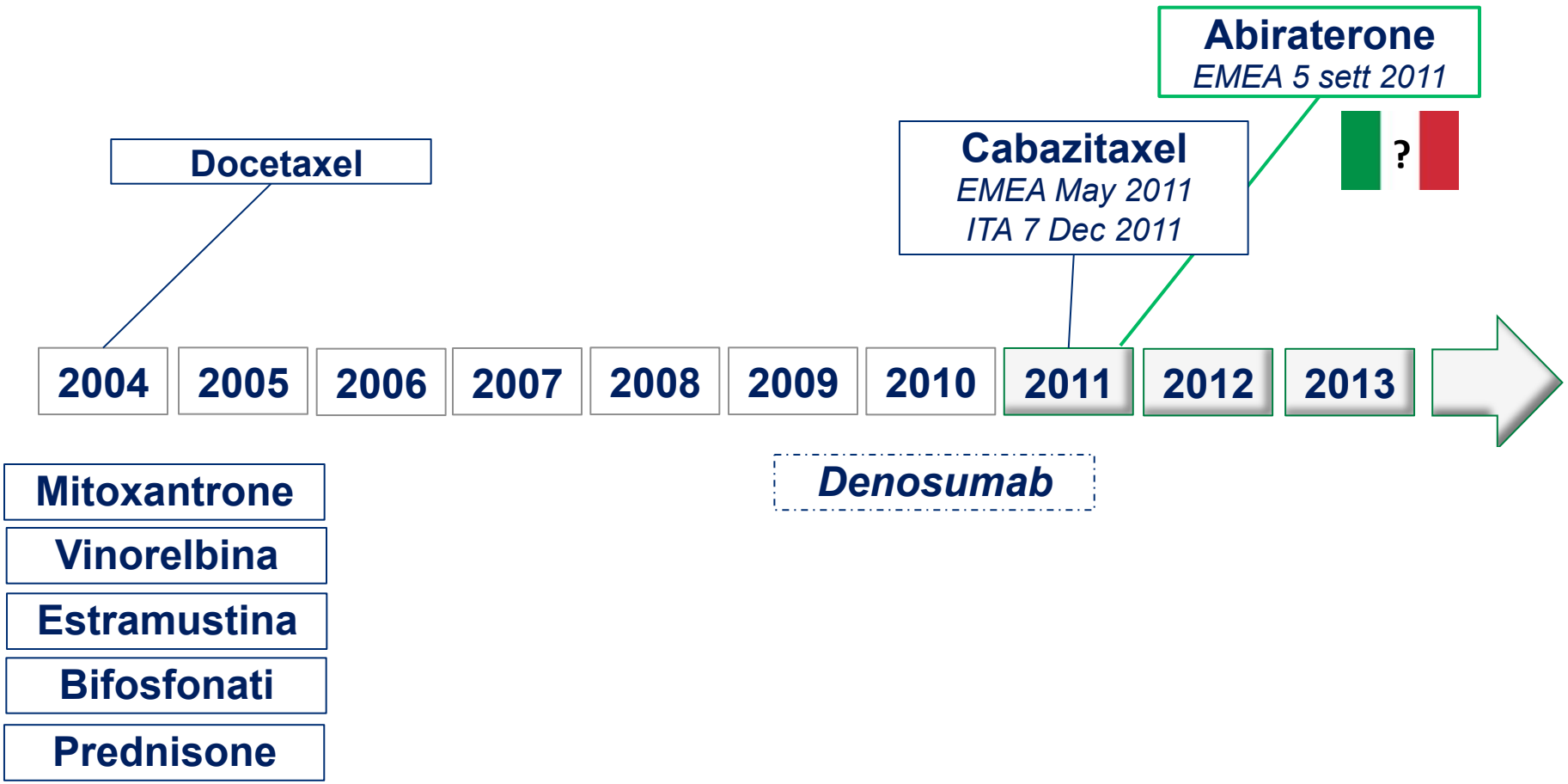
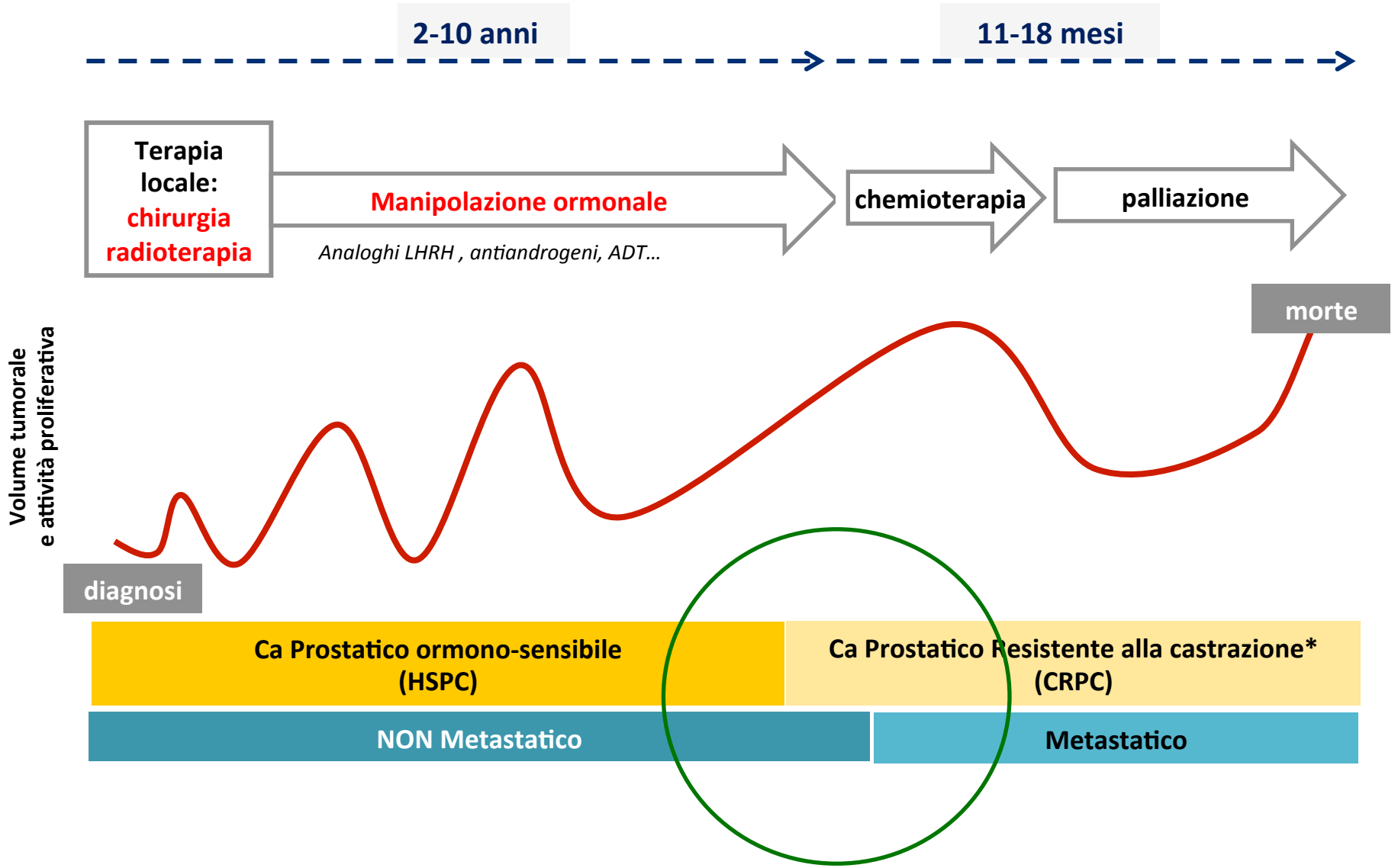
CRPC: dove stiamo andando?
Terapie in fase di approvazione e future per il CRPC



Schematizzazione del decorso clinico del Carcinoma della Prostata



Da HSPC a CRPC: cosa abbiamo imparato?

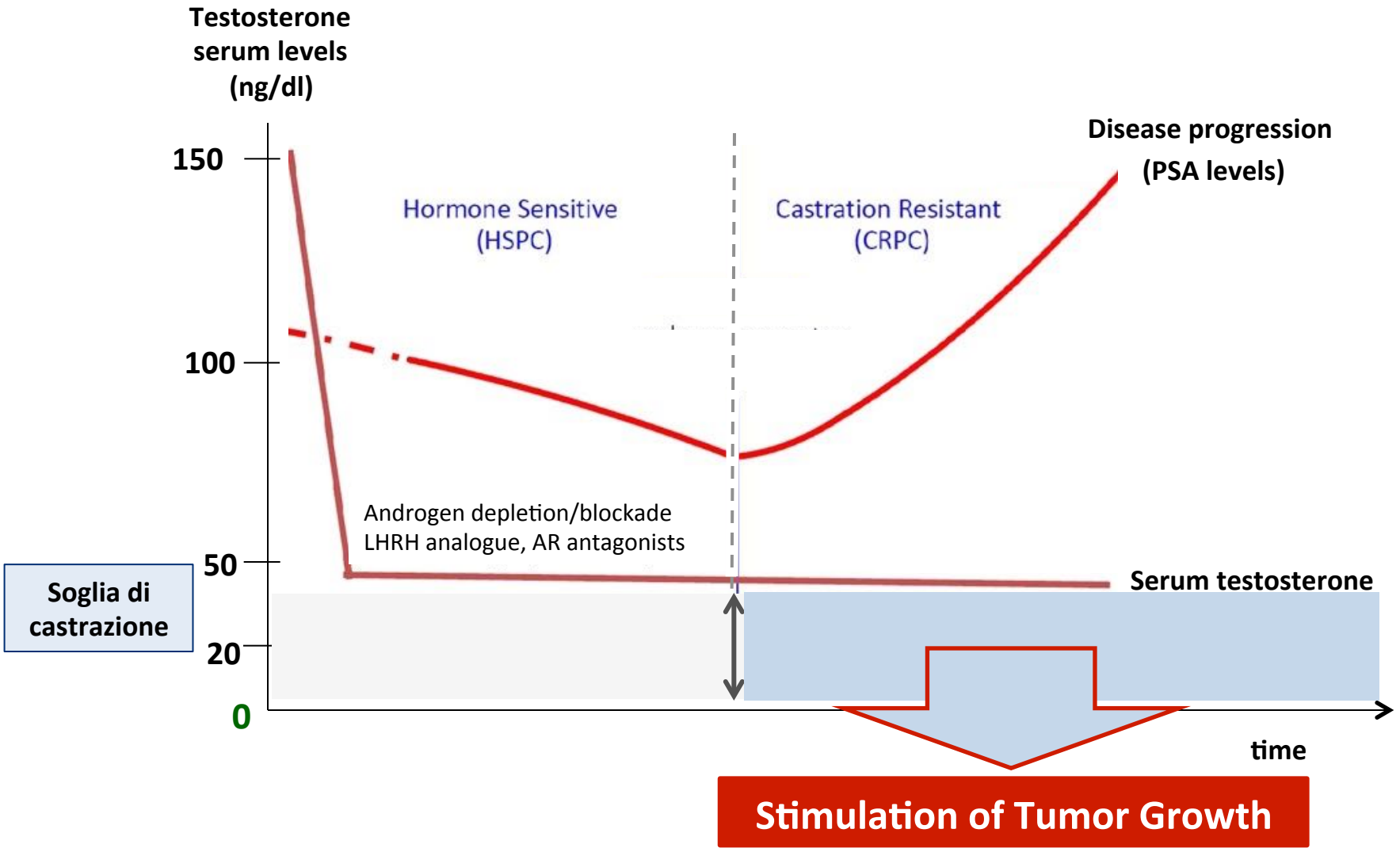
- **Storica concezione**

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

- **Nuova concezione**

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

Nel CRPC il residuo di T circolante post-ADT stimola la crescita tumorale



Mod. da De Bono ESMO Educational Program, Genitourinary Cancers 2010 modified

Mol Cell Endocrinol. 2008 Nov 25;295(1-2):115-20. Epub 2008 Aug 20.

Androgen-independent prostate cancer cells acquire the complete steroidogenic potential of synthesizing testosterone from cholesterol.

Dillard PR, Lin MF, Khan SA.
Department of Biological Sciences, Clark Atlanta University, Atlanta, GA 30314, United States.

Biosintesi androgeni

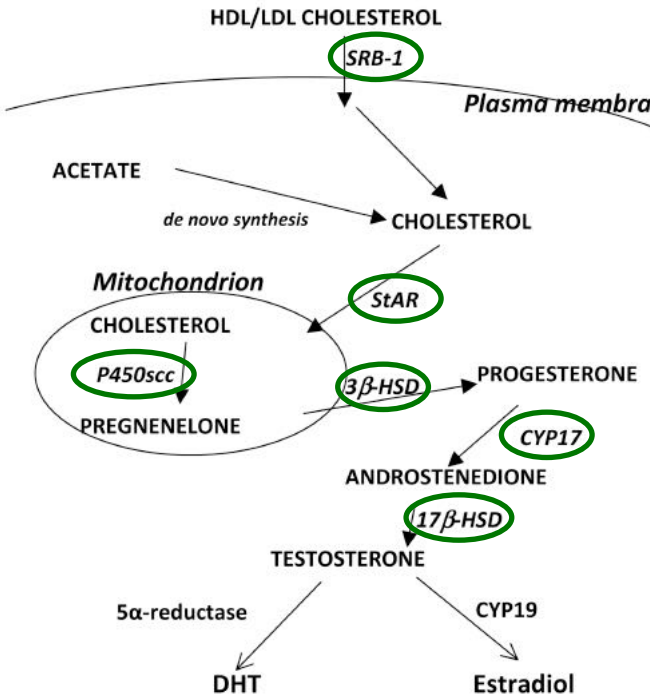
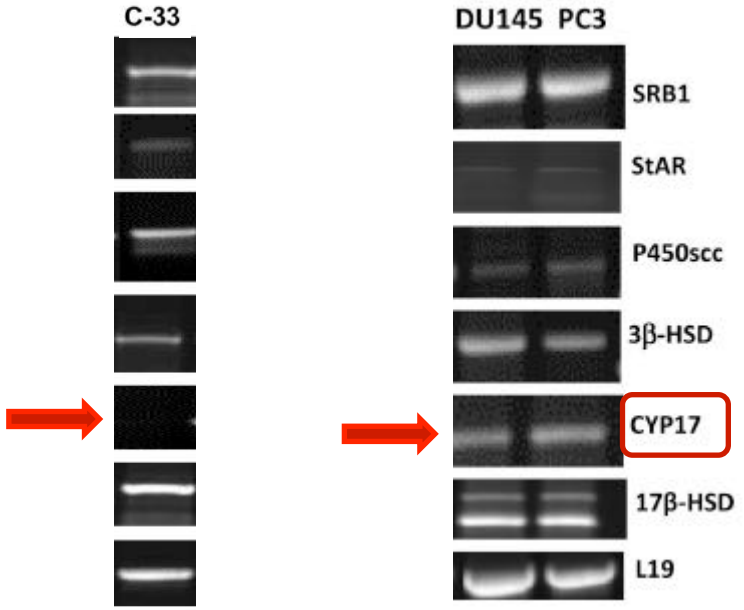


Fig 1.
Diagram illustrating pathways involved in biosynthesis and metabolism of testosterone.

Cellule tumore prostata ormono sensibili

Cellule tumore prostata CRPC



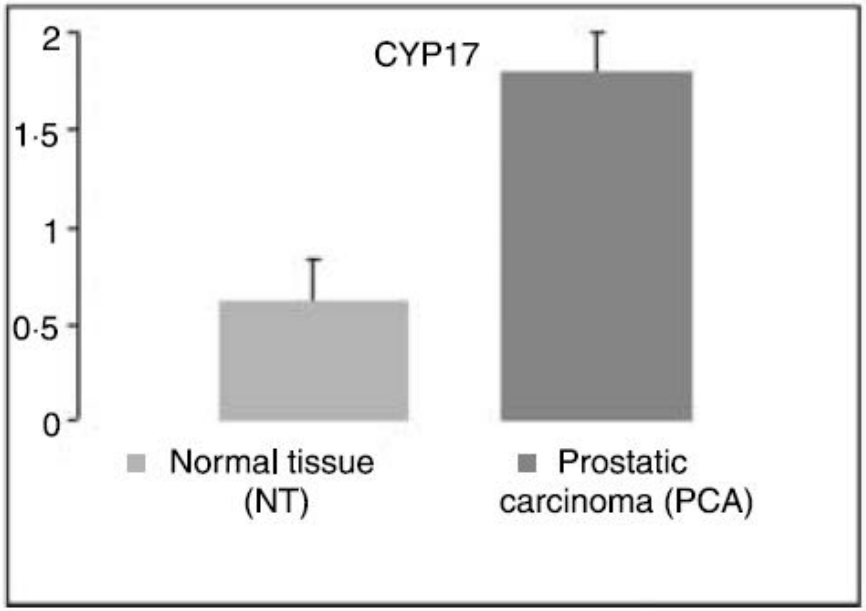
RT-PCR su mRNA

Mod. Da Dillart et al, Mol cell Endocrinol, 2008

Le cellule di carcinoma prostatico metastatico iperesprimono CYP17

Increased metastatic lymph node 64 and CYP17 expression are associated with high stage prostate cancer

A Stigliano[1,3], O Gandini[2], L Cerquetti[1,3], P Gazzaniga[2], S Misiti[1,3], S Monti[1], A Gradilone[2], P Falasca[1], M Poggi[1], E Brunetti[3], A M Aglianò[2] and V Toscano[1]



(C) The results of densitometric analysis of all samples studied are reported. Bars represent mean values of 60 normal tissues and 60 prostate carcinomas. The statistical analysis was performed by paired *t*-test ($P<0{\cdot}002$).

Stigliano et al, Journal of Endocrinology 2007

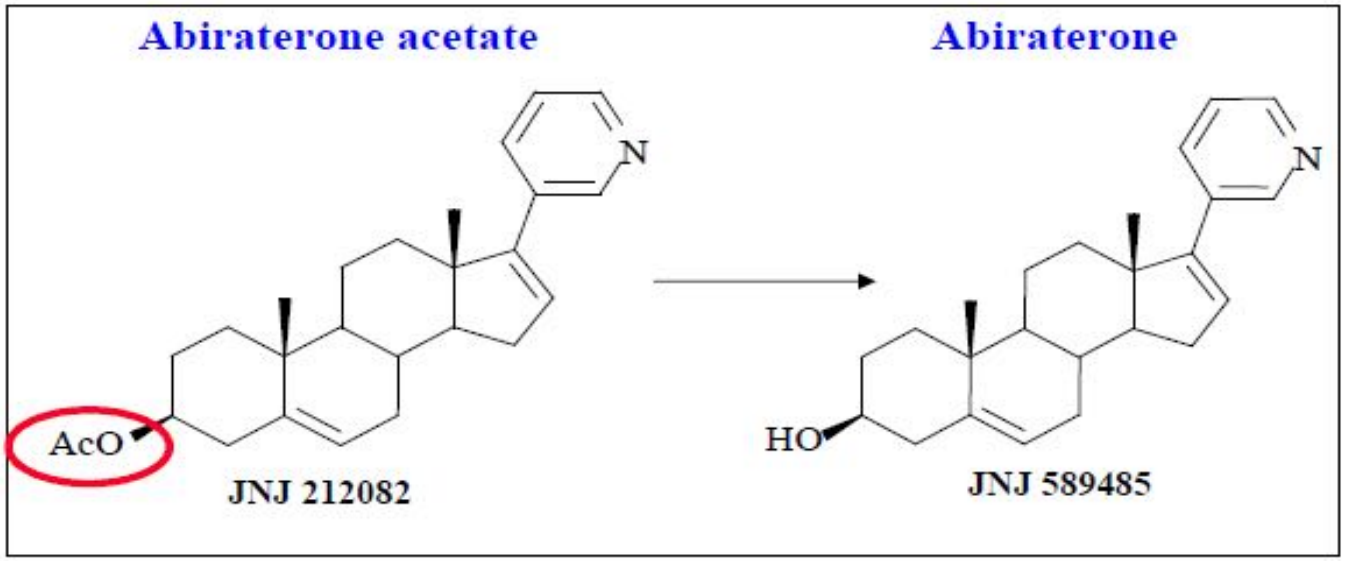
Il livello di iperespressione di CYP17 correla con lo stadio di malattia e con il Gleason

(B) Clinicopatho-logical features	CYP17 low expression	CYP17 high expression	*P* value
Stage			
II	22/22 (100%)	0/22 (0%)	<0·005
III	8/20 (40%)	12/20 (60%)	
IV	1/18 (5%)	17/18 (95%)	
Gleason			
<4	4/4 (100%)	0/4 (0%)	<0·005
4–7	24/27 (89%)	3/27 (11%)	
>7	3/29 (10%)	26/29 (90%)	

Stigliano et al, Journal of Endocrinology 2007

Abiraterone Acetato

Inibitore ad alta affinità selettivo ed irreversibile del citocromo CYP17 *(P450c17)*



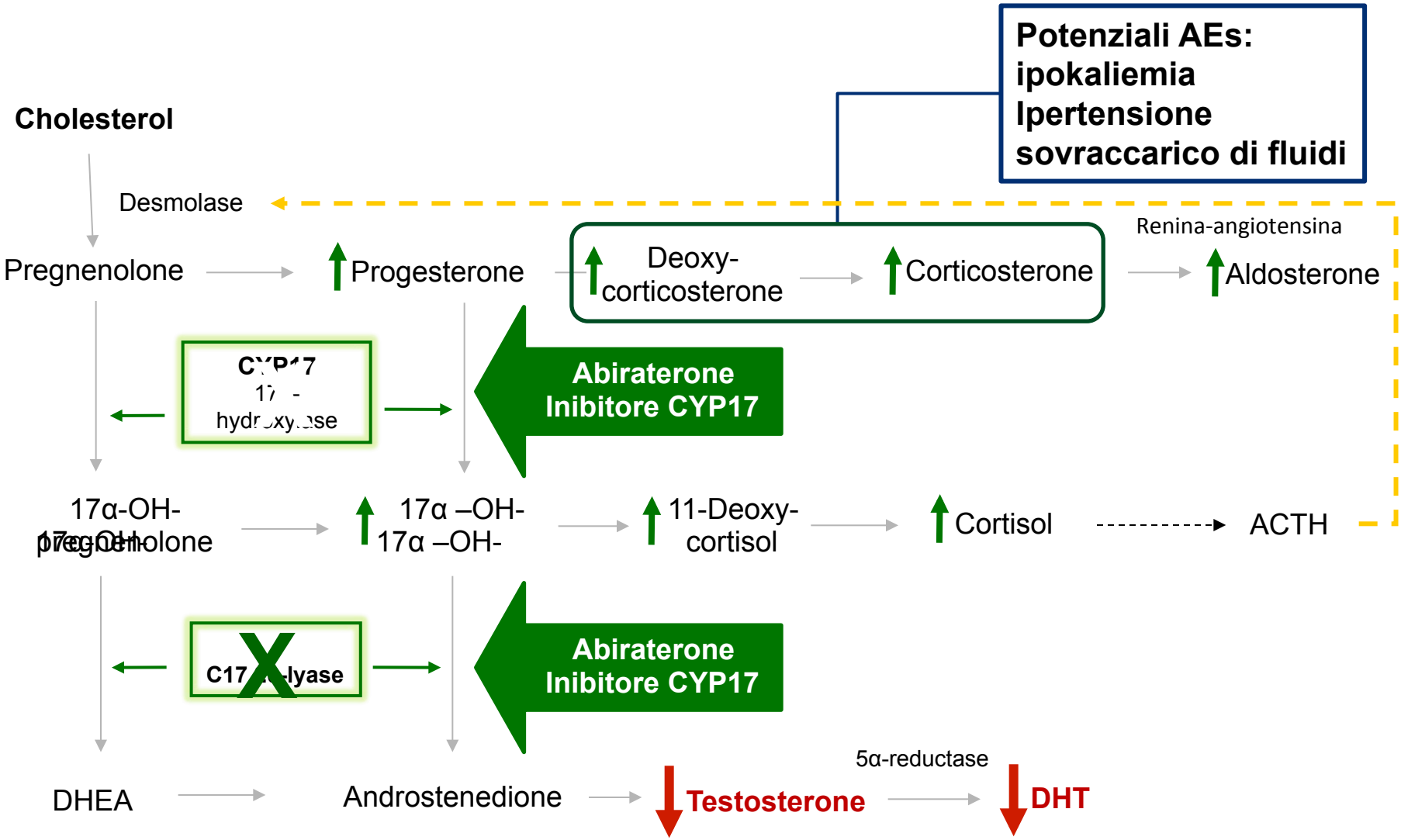
Composto di sintesi derivato dal pregnenolone

http://www.ema.europa.eu/docs/it_IT/document_library/EPAR_-_Product_Information/human/002321/WC500112858.pdf

Abiraterone: una nuova entità terapeutica

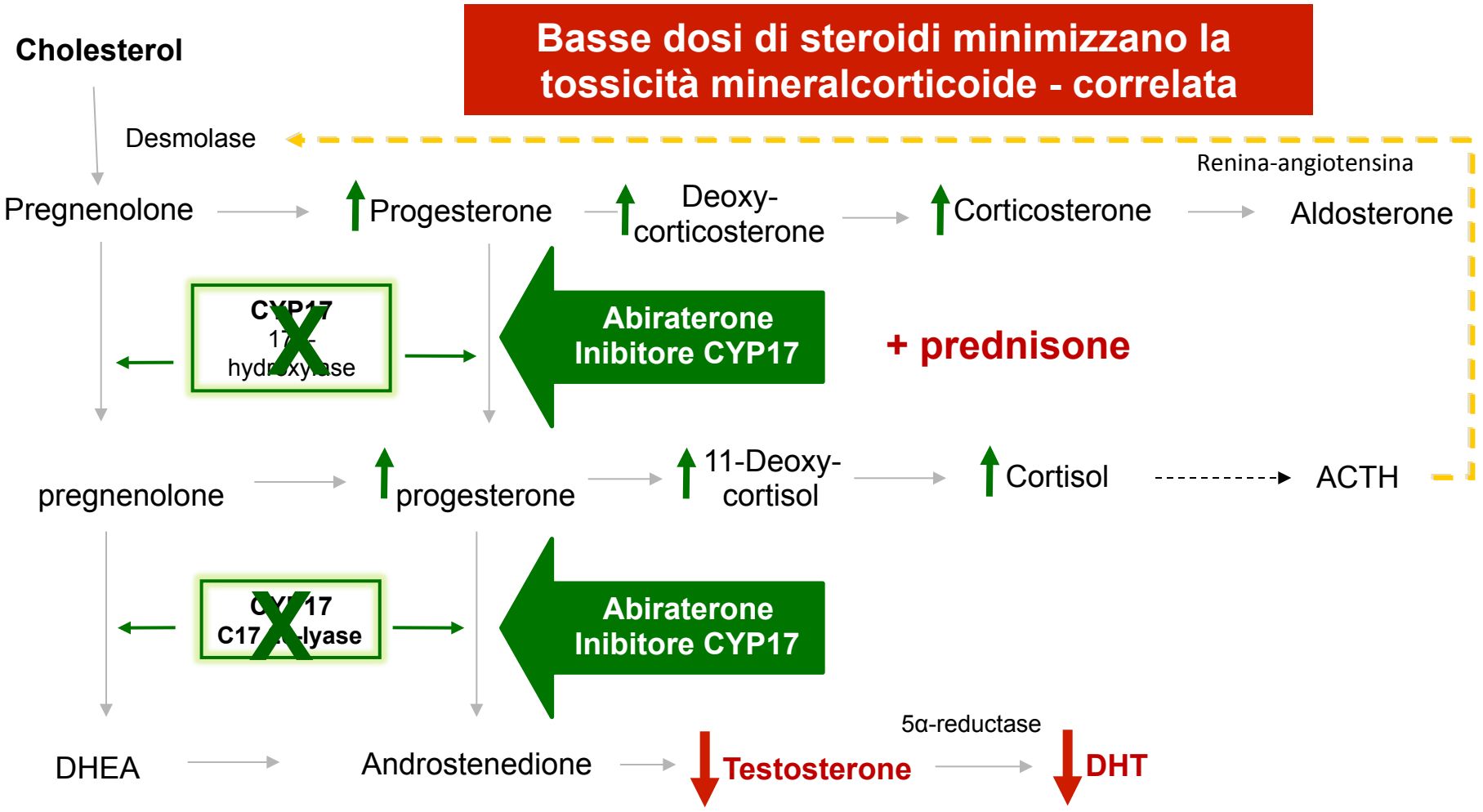
- **Primo di una nuova sotto-classe farmacologica**
  - **Nuovo meccanismo d'azione**: inibitore biosintesi del testosterone mediante **inibizione CYP17**
  - **Codice ATC L02BX03** *(antagonisti ormonali ed altri agenti correlati)*
- **Prolunga la OS nei pazienti CRPC post-docetaxel**
  - **Primo agente non chemioterapico** in questo setting di pazienti
- **Maneggevolezza e comodità d'uso**
  - **Primo agente orale in questo setting di pazienti**
  - **Favorevole profilo di tollerabilità**, limitata tossicità G 3-4, eventi correlati al MoA principalmente di G1,2

Abiraterone inibisce la sintesi del testosterone tramite inibizione



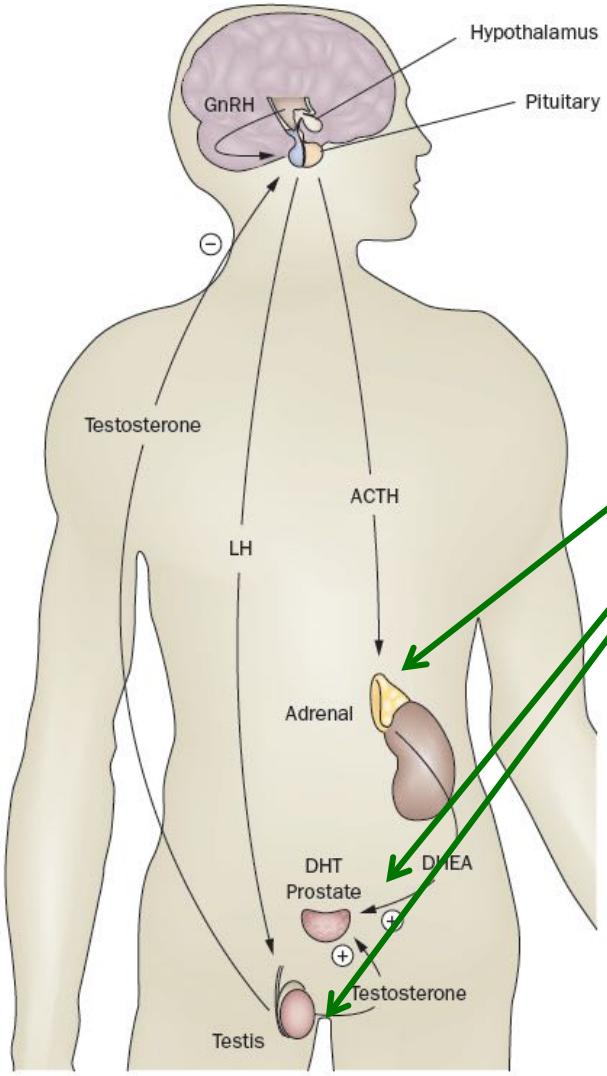
Yang, Drugs. 2011; Attard, JCO 2008

del testosterone tramite inibizione di CYP17



Yang, Drugs. 2011; Attard, JCO 2008

Abiraterone blocca la sintesi degli androgeni in tutti i possibili siti di produzione



Abiraterone:
INIBIZIONE di CYP17

Inibizione sintesi testosterone nei testicoli, surrene e nelle cellule tumorali

Testosteronemia ≤1 ng/dl

Blocco produzione di T nelle cellule tumorali (autoalimentazione)

NO testosterone nel microambiente tumorale

apoptosi cellule tumorali in qualunque sede

Abiraterone: studio registrativo

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 26, 2011 VOL. 364 NO. 21

Abiraterone and Increased Survival in Metastatic Prostate Cancer

Johann S. de Bono, M.B., Ch.B., Ph.D., Christopher J. Logothetis, M.D., Arturo Molina, M.D., Karim Fizazi, M.D., Ph.D., Scott North, M.D., Luis Chu, M.D., Kim N. Chi, M.D., Robert J. Jones, M.D., Oscar B. Goodman, Jr., M.D., Ph.D., Fred Saad, M.D., John N. Staffurth, M.D., Paul Mainwaring, M.D., M.B., B.S., Stephen Harland, M.D., Thomas W. Flaig, M.D., Thomas E. Hutson, D.O., Pharm.D., Tina Cheng, M.D., Helen Patterson, M.D., John D. Hainsworth, M.D., Charles J. Ryan, M.D., Cora N. Sternberg, M.D., Susan L. Ellard, M.D., Aude Fléchon, M.D., Ph.D., Mansoor Saleh, M.D., Mark Scholz, M.D., Eleni Efstathiou, M.D., Ph.D., Andrea Zivi, M.D., Diletta Bianchini, M.D., Yohann Loriot, M.D., Nicole Chieffo, M.B.A., Thian Kheoh, Ph.D., Christopher M. Haqq, M.D., Ph.D., and Howard I. Scher, M.D., for the COU-AA-301 Investigators*

Abiraterone: studio registrativo

(147 siti in 13 Paesi; USA, Europa, Australia, Canada)

- **1195 pts con mCRPC in progressione**
- **Fallimento 1 o 2 precedenti regimi di CT, uno dei quali a base Docetaxel**
- **Randomizzazione 2:1**
- **Stratificazione per:**
- ECOG PS (0-1 vs. 2)
- Maggior intensità di dolore nelle ultime 24 ore (BPI short form; 0-3 [assente] vs. 4-10 [presente])
- **Precedente chemioterapia** (1 vs. 2)
- Tipo di progressione (solo PSA vs. Rx PD con o senza PSA PD)

Abiraterone acetate 1000 mg QD

Prednisone 5 mg BID

Placebo QD

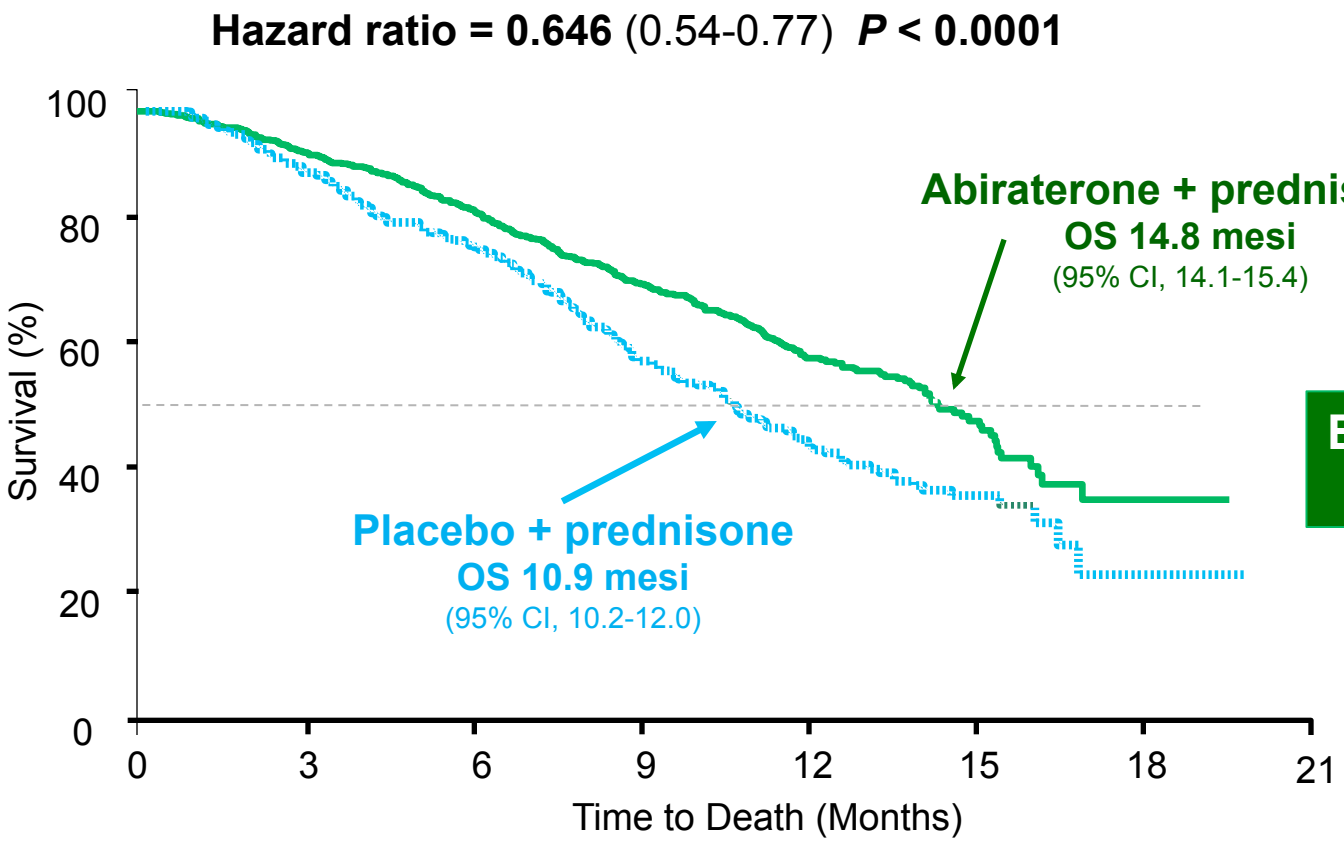
Prednisone 5 mg BID

TRATTAMENTO A PROGRESSIONE

Obiettivo primario: **Sopravvivenza globale** (miglioramento del 25%; HR 0.8)

Mod. da De Bono et al. NEJM vol. 364 n° 21 - 2011

AA: prima analisi dimostra prolungamento significativo della sopravvivenza nel mCRPC



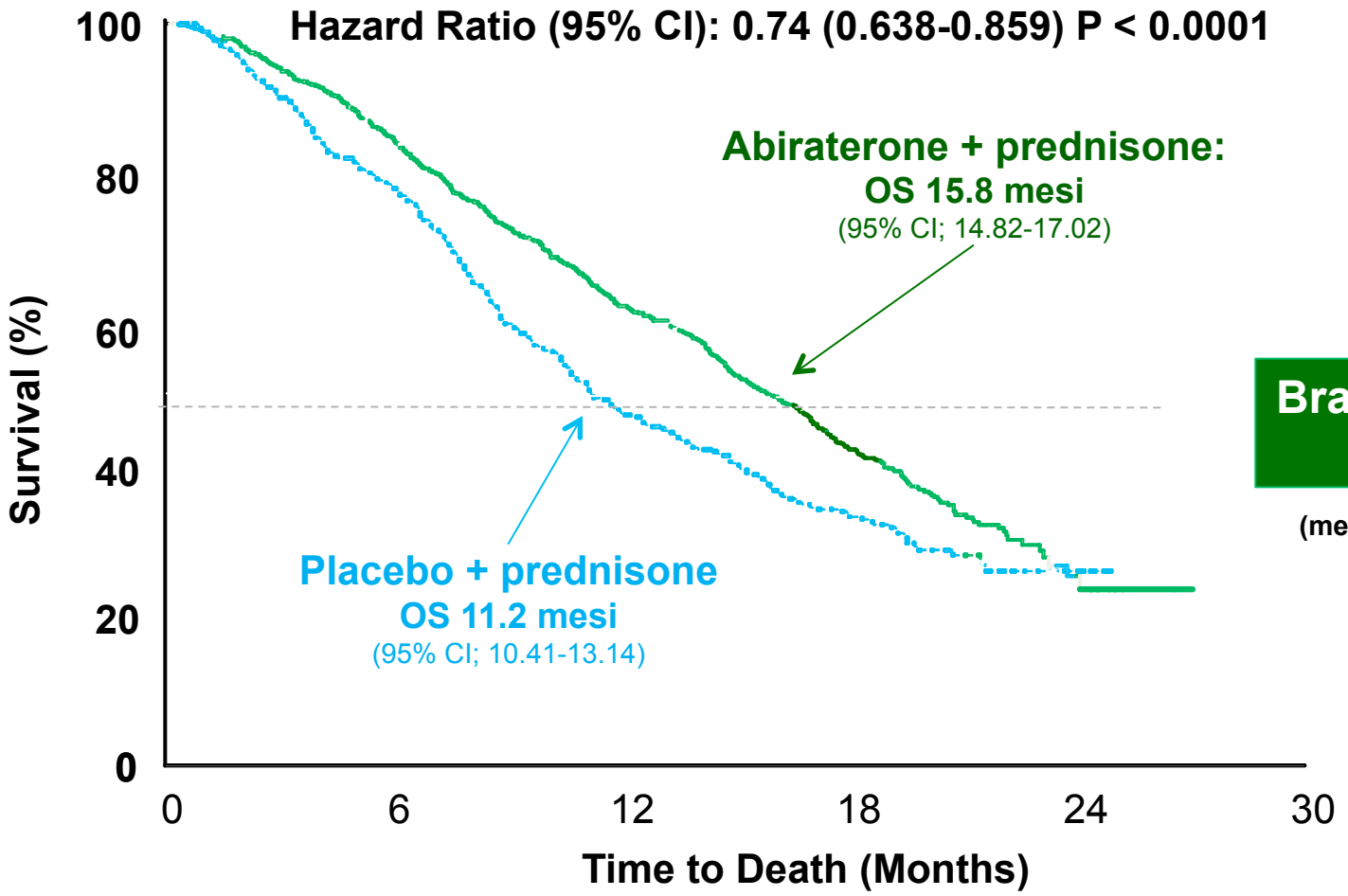
AA/Pdn	797	736	657	520	282	68	2	0
Placebo/Pdn	398	355	306	210	105	30	3	0

Braccio Abiraterone + 3.9 mesi

(median follow up: 12,8 mesi)

de Bono et al. NEJM 2011

AA prolungamento significativo della sopravvivenza nel mCRPC



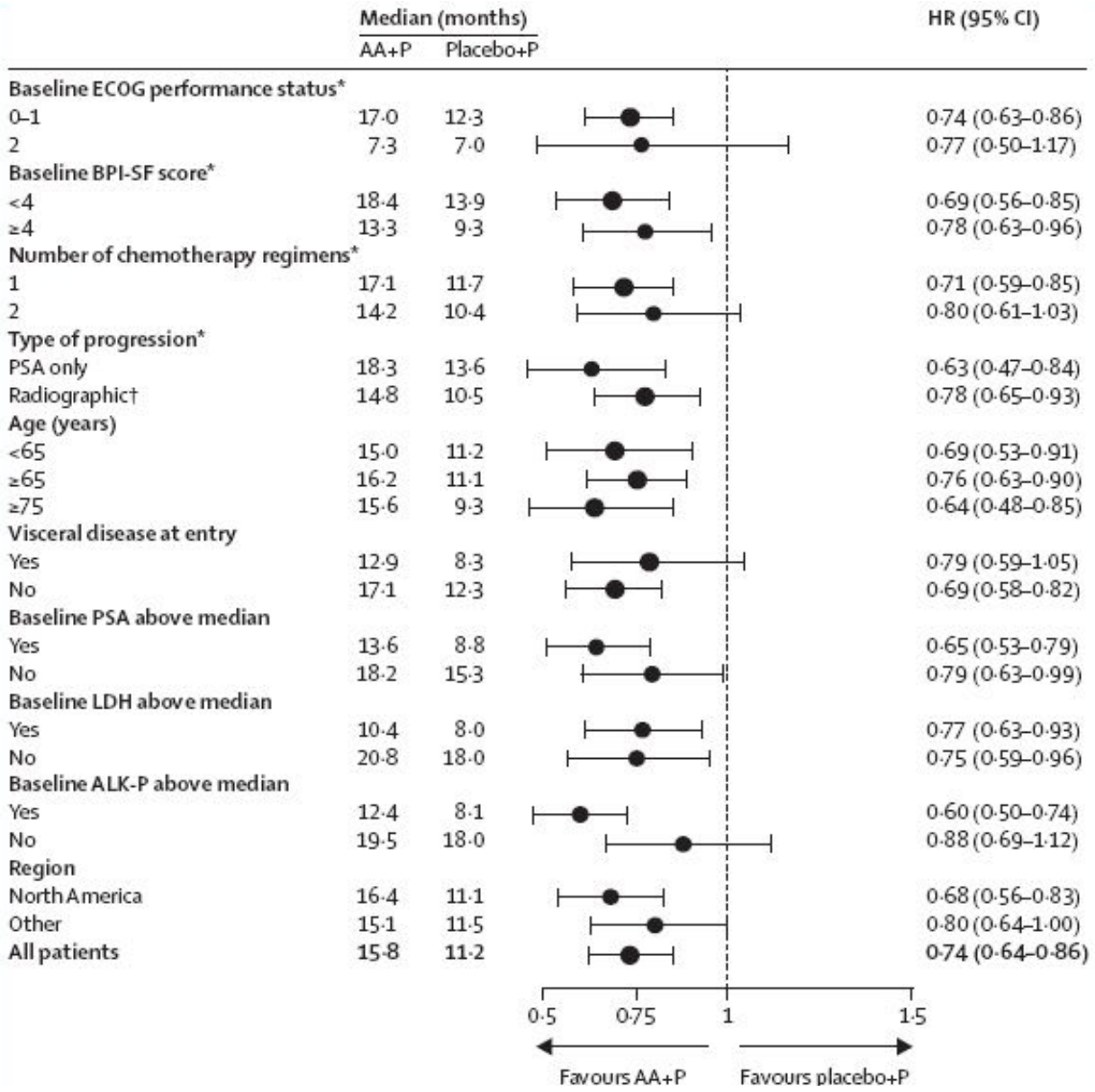
Braccio Abiraterone + 4.6 Mesi

(median follow up: 20,2 mesi)

second pre-planned analysis (775 Events)

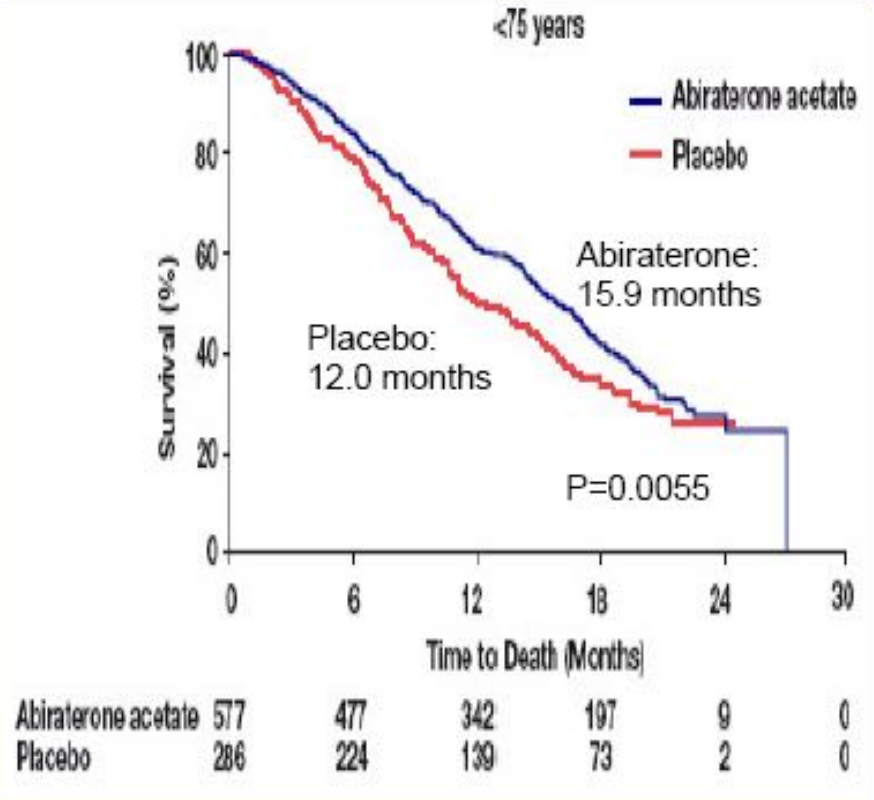
Scher et al. JCO 2011; 29 (

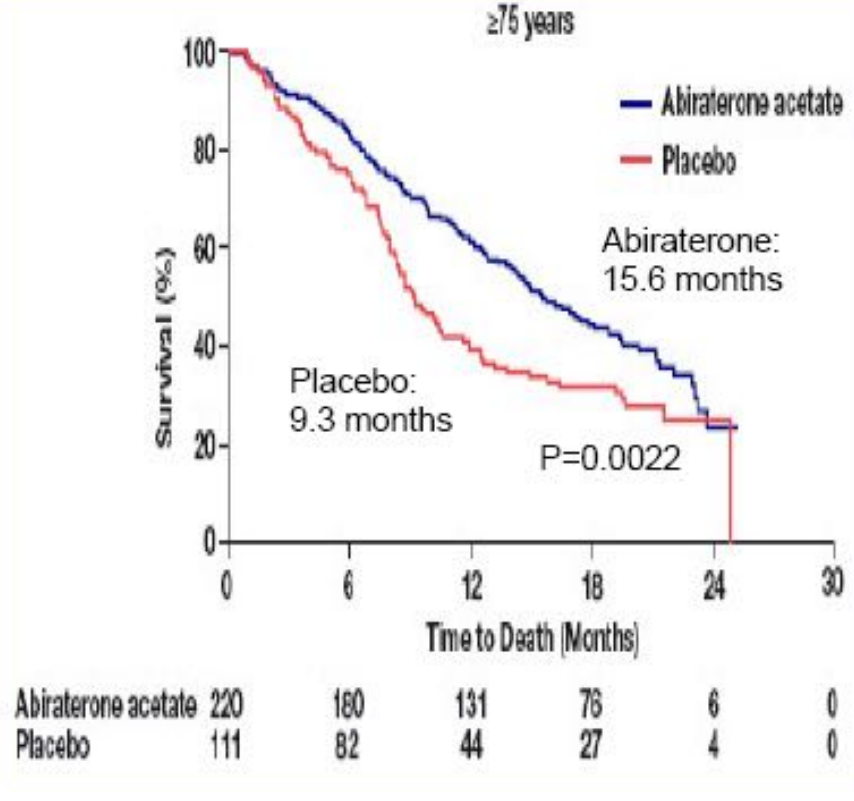
Analisi per sottogruppi:dato aggiornato



Fizazi et al.www.thelancet.com/oncology Published online September 18, 2012

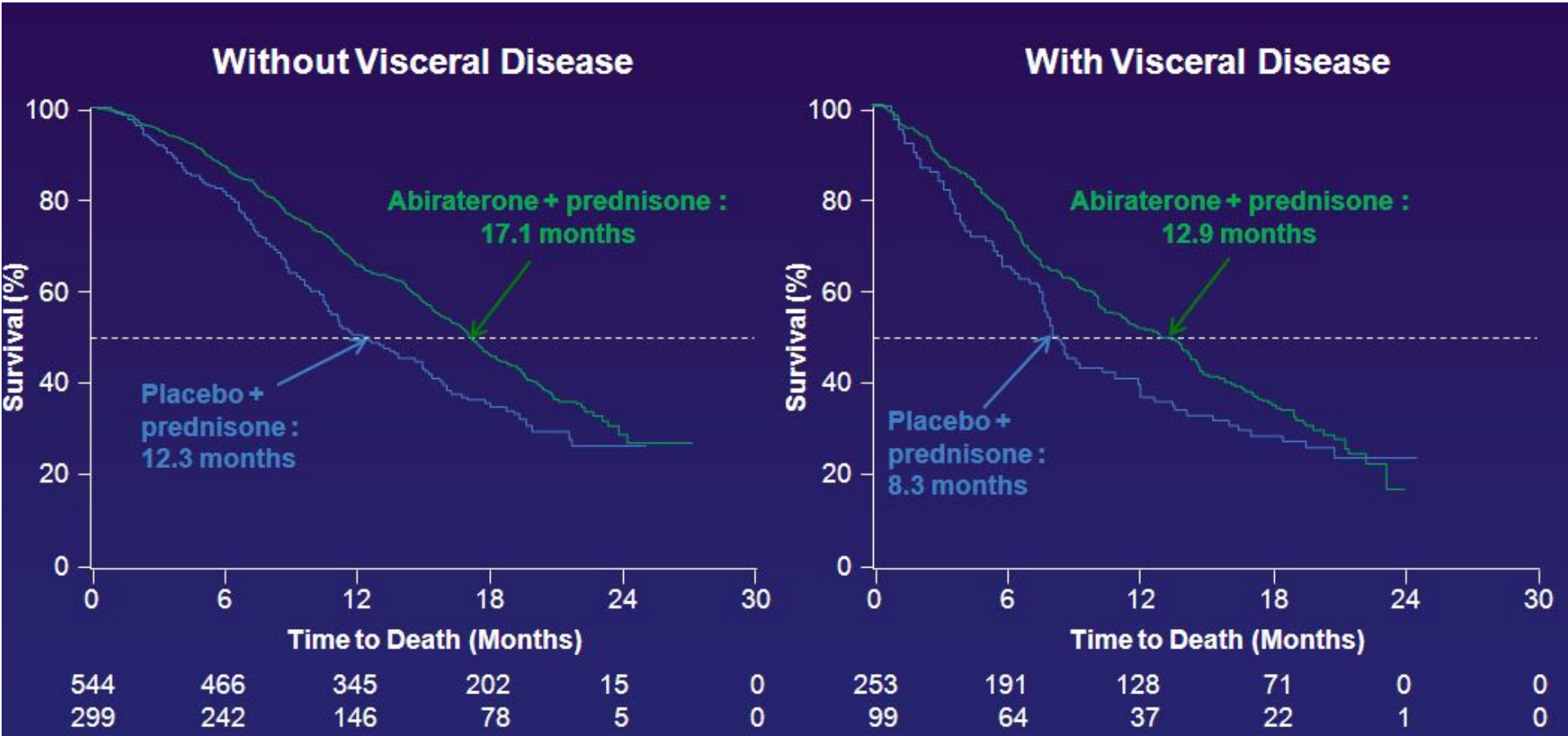
OS nei pazienti over 75: EAU 2012





Mulders et al; EAU 2012; abs 127; poster presentation

OS and visceral disease



Median OS – Abiraterone + prednisone vs. Placebo + prednisone:

Without visceral disease: 17.1 vs. 12.3 months (HR = 0.69; 95% CI: 0.58-0.82)

With visceral disease: 12.9 vs. 8.3 months (HR = 0.79; 95% CI: 0.59-1.05)

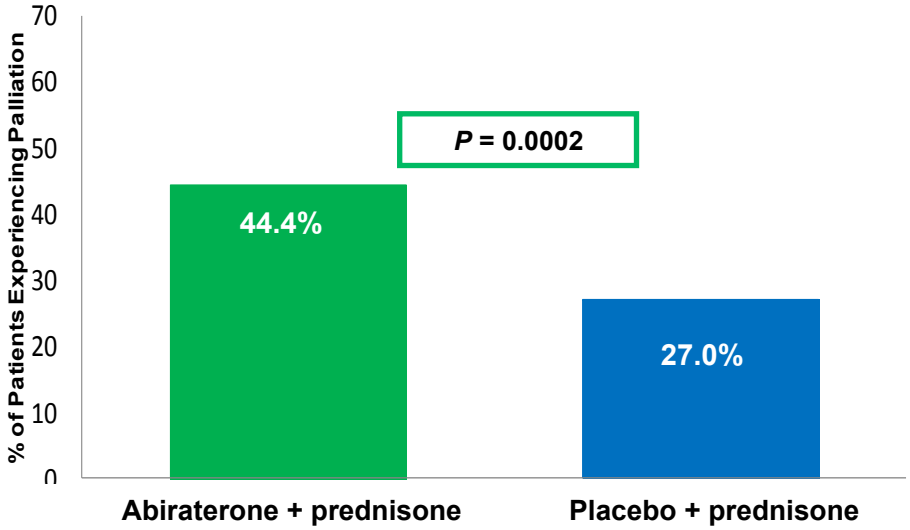
Fizazi et al. ECCO 2011: Abstract 7000 (oral presentation)

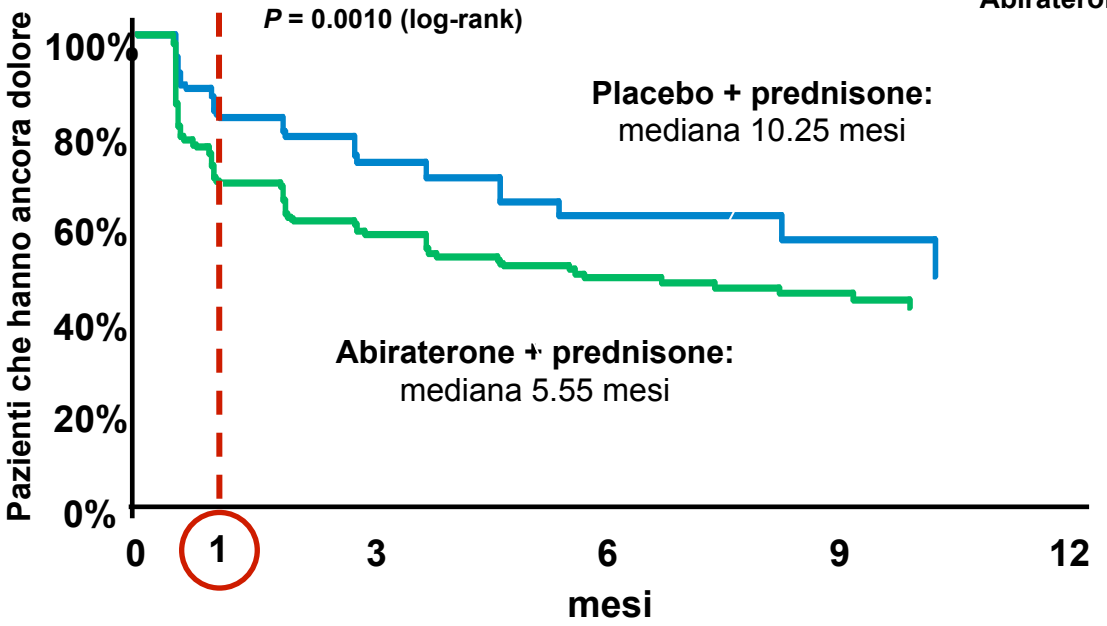
End Points Secondari

	Abiraterone + prednisone (n = 797)	Placebo + prednisone (n = 398)	HR 95% CI	P Value
TTPP (mesi)	10.2	6.6	0.58 (0.46, 0.73)	< 0.0001
rPFS (mesi)	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

Mod. da De Bono et al. NEJM vol. 364 n° 21 -

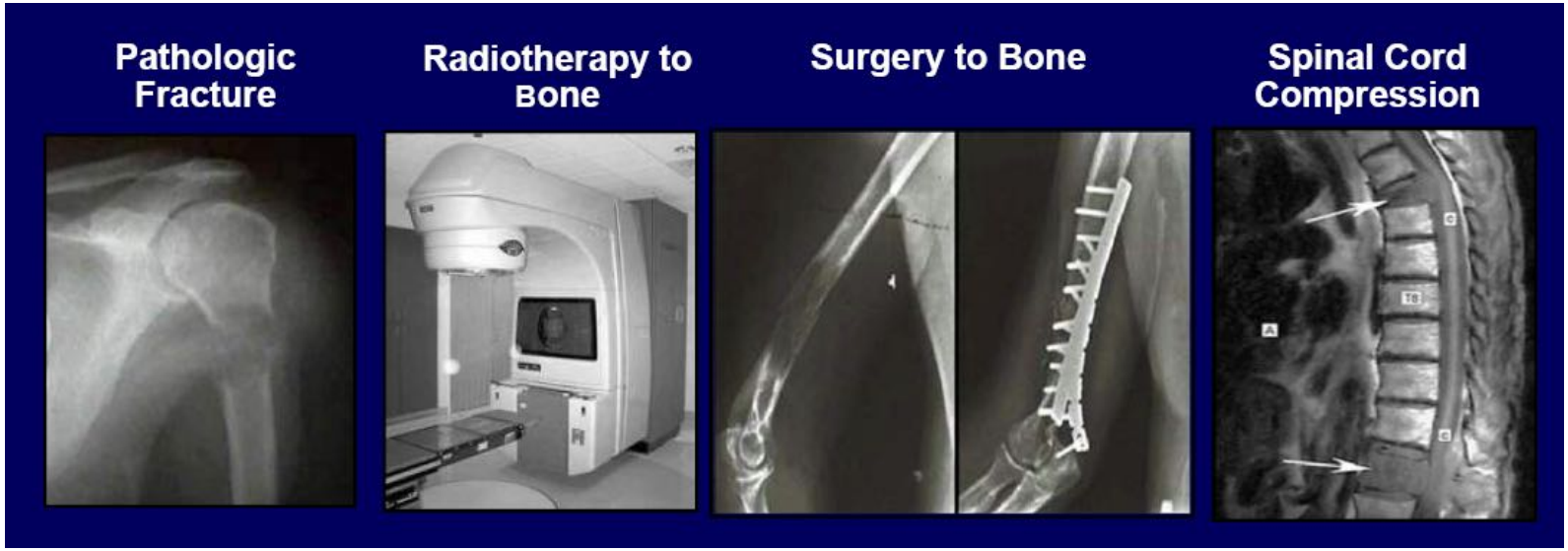
Riduzione Intensità del Dolore Sintomatico osservata dal primo mese





Logothetis et al. JCO 2011; 29 (Suppl): Abst4520

Tempo al primo evento scheletrico (SRE)



Tempo al primo evento scheletrico (SRE)

	Abiraterone + prednisone (n = 797)	Placebo + prednisone (n = 398)	P Value
25° percentile, giorni	**301.0**	150.0	< 0.0001
	10 mesi	5 mesi	

Logothetis et al. JCO 2011; 29 (Suppl): Abst 4520

Tossicità limitata di grado 3/4 e sovrapponibile a controllo

	Abiraterone + prednisone (N=791)			Placebo + prednisone (N=394)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	%	%	%	%	%	%
Anemia	23	**6**	**1**	26	**6**	**2**
Thrombocytopenia	4	**1**	**<1**	3	**<1**	**<1**
Neutropenia	1	**<1**	**0**	1	**1**	**0**
Febrile neutropenia	0	**0**	**0**	0	**0**	**0**
Diarrhea	18	**1**	**0**	14	**1**	**0**
Fatigue	44	**8**	**<1**	43	**9**	**1**
Asthenia	13	**2**	**0**	13	**2**	**<1**
Back pain	30	**6**	**<1**	33	**9**	**<1**
Nausea	30	**2**	**<1**	32	**3**	**0**
Vomiting	21	**2**	**<1**	25	**3**	**0**
Hematuria	8	**1**	**0**	8	**2**	**0**
Abdominal pain	12	**2**	**0**	11	**2**	**0**
Pain in arm or leg	17	**2**	**<1**	20	**5**	**0**
Dyspnea	13	**1**	**<1**	12	**2**	**<1**
Constipation	26	**1**	**0**	31	**1**	**0**
Pyrexia	9	**<1**	**0**	9	**1**	**0**
Arthralgia	27	**4**	**0**	23	**4**	**0**
Urinary tract infection	12	**2**	**0**	7	**<1**	**0**
Pain	2	**1**	**0**	5	**2**	**<1**
Bone pain	25	**5**	**<1**	28	**6**	**1**

de Bono et al. N Engl J Med 2011

AEs di particolare interesse per abiraterone

	Abiraterone + Pdn (n = 791)			Placebo + Pdn (n = 394)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Ritenzione idrica e edema	31%	**2%**	**<1%**	22%	1%	0
Ipokaliemia	17%	**3%**	**<1%**	8%	1%	0
Disordini cardiaci	13%	**3%**	**1%**	11%	2%	<1%
Alterazioni funzionalità epatica	10%	**3%**	**<1%**	8%	3%	<1%
Ipertensione	10%	**1%**	**0**	8%	<1%	0

de Bono et al. N Engl J Med 2011; 346(21): 1995-2005

Conclusioni studio Abiraterone

- Prolungamento dell' OS nei pazienti con mCRPC in progressione dopo chemioterapia a base di docetaxel

  Miglioramento della sopravvivenza mediana di 4.6 mesi

- Miglioramento significativo di TTPP, rPFS, e PSA

- Rapido miglioramento dei sintomi osseo-correlati

- Favorevole profilo di sicurezza senza la tossicità tipica dei chemioterapici

- Miglioramento significativo della QoL

de Bono et al. Ann Oncol 2010: Abstract LBA5 (Oral presentation at ESMO)
Scher et al. J Clin Oncol 2011; 29(7S):Abstract 4 (Oral presentation at ASCO GU)
De Bono NEJM 2011

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

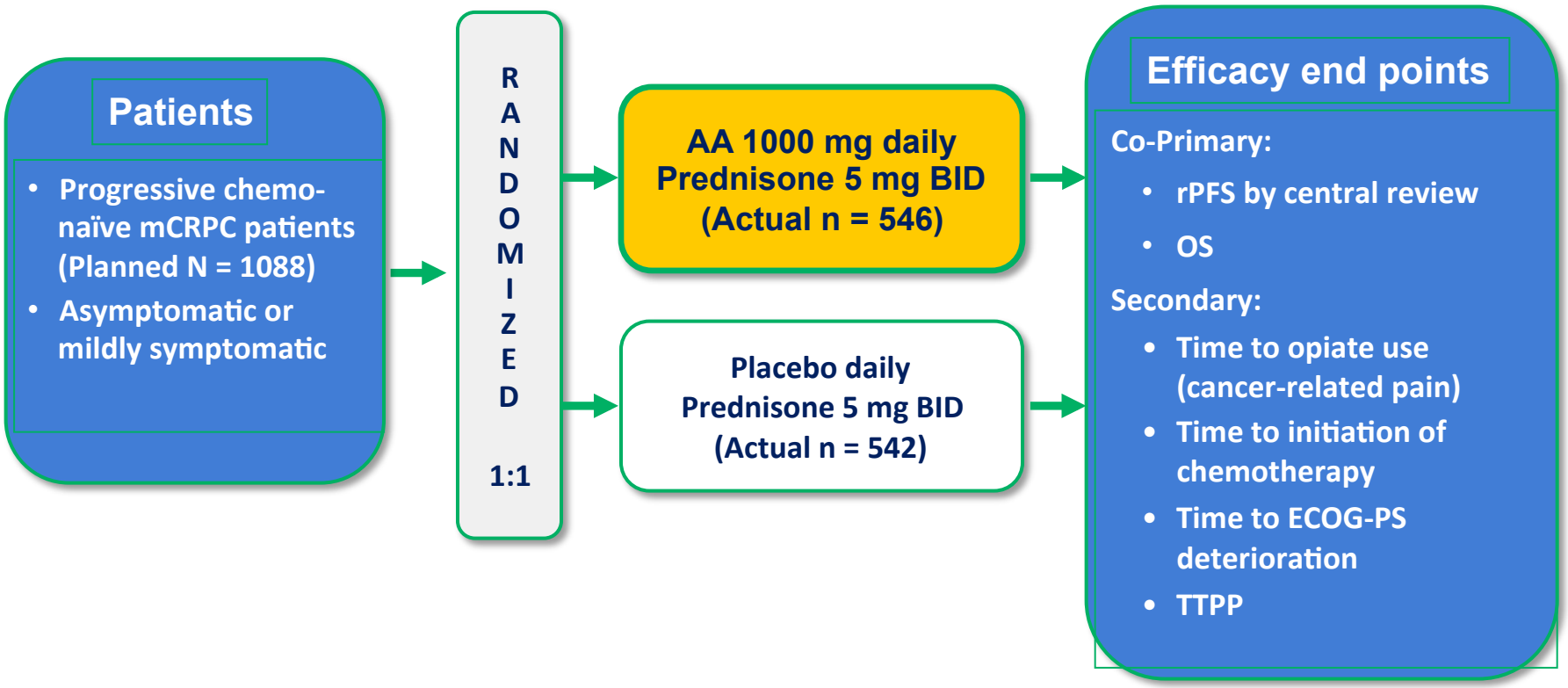
Final appraisal determination

Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen

"...The Committee therefore recommended abiraterone in combination with prednisolone or prednisone as an option for the treatment of castration-resistant metastatic prostate cancer that has progressed after one docetaxel-containing chemotherapy regimen.....The Committee concluded that abiraterone offers a step change in treatment because it is an oral drug taken by patients at home, and is associated with few adverse reactions...."

Abiraterone in pre-chemioterapia

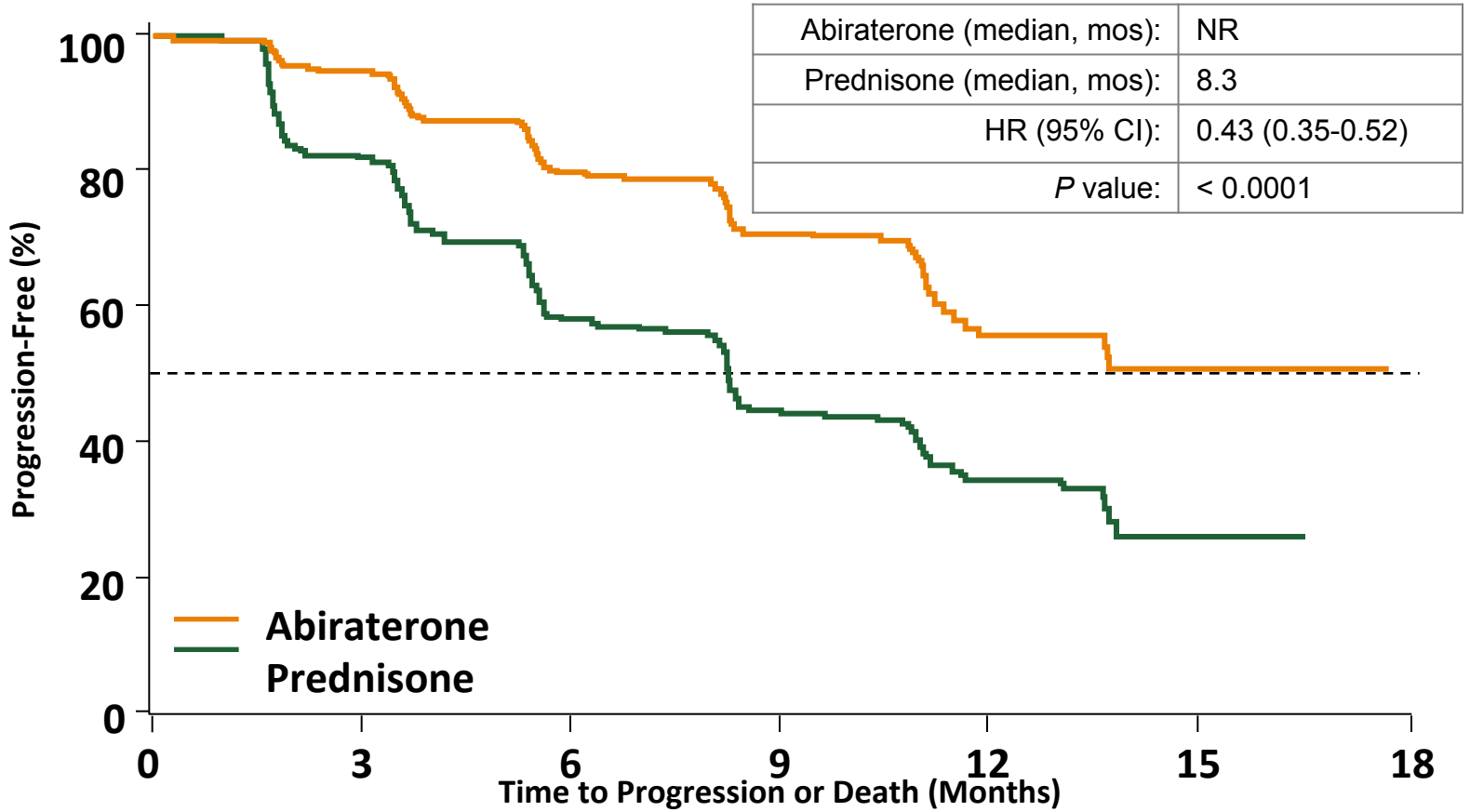
Overall Study Design of COU-AA-302



- **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. ASCO 2012; Abstract LBA4518 (Oral Presentation

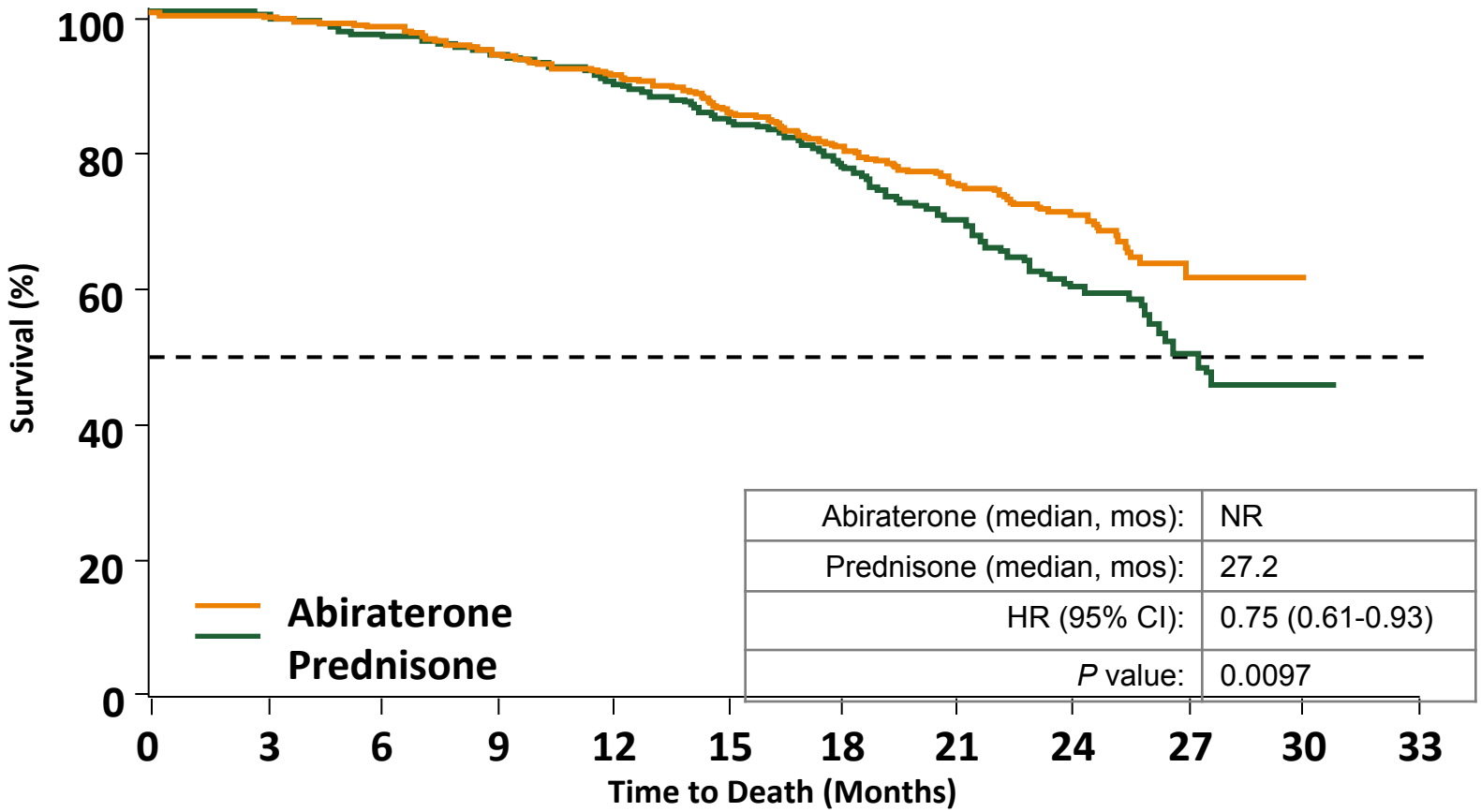
Statistically Significant Improvement in rPFS
Primary End Point – Independent Review



Abiraterone	546	489	340	164	46	12	0
Prednisone	542	400	204	90	30	3	0

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation

Strong Trend in OS Primary End Point



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

Abiraterone	546	538	524	503	482	452	412	258	120	27	0	0
Prednisone	542	534	509	493	465	437	387	237	106	25	2	0

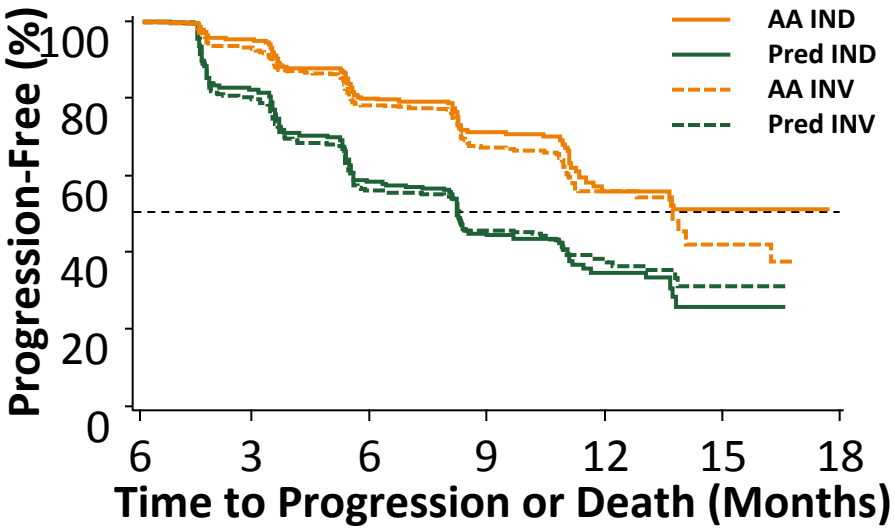
Prespecified signifi

L'attesa nell'apertura del cieco avrebbe comportato un ritardo nella disponibilità del farmaco per i pazienti

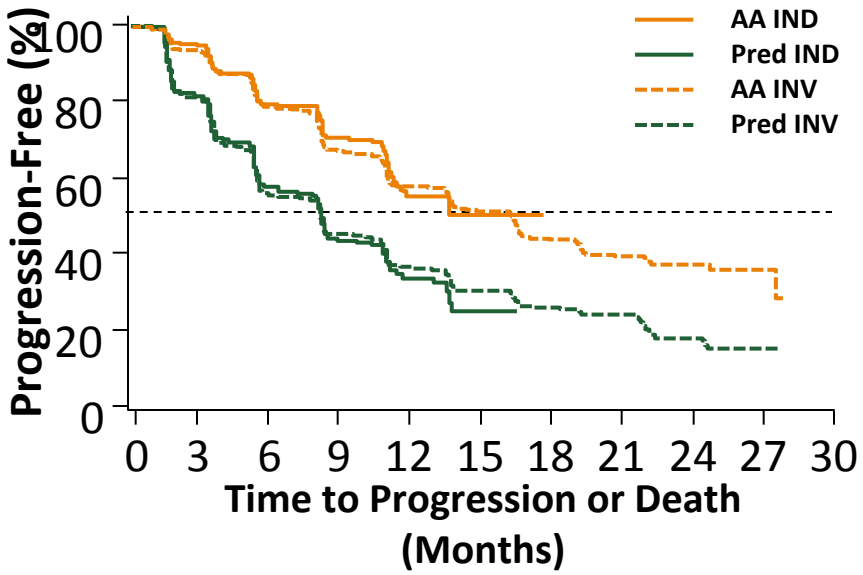
Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation

rPFS Was Highly Consistent Between Independent and Investigator Reviews

IND 2010 – INV 2010



IND 2010 – INV 2011



- Agreement between independent and investigator assessment on rPFS event status was observed (abiraterone group, 430/546 [79%]; prednisone group, 414/542 [76%])*

*based on the IND 2010 – INV 2010 analysis

IND, independent review; INV, investigator review

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation

Positive Association of rPFS With OS

Association of rPFS and OS at Dec 2011 Interim Analysis*
0.72

Spearman Rho (r)	Level of Association
-1	Negatively associated
0	No association
1	Positively associated

Robust association between rPFS and OS provides possible support for use of rPFS adapted from PCWG2 criteria as

- –Outcome measure of OS
- –Primary/co-primary end point in phase 3 mCRPC studies

•*Per Spearman's correlation coefficient estimated through Clayton copula

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

Statistically Significant Improvement in All Secondary End Points

	AA + Predn	Plac + Predn		
	Median (months)	Median (months)	HR (95% CI)	P Value
Time to opiate use (cancer related pain)	**NR**	**23.7**	0.69 (0.57, 0.83)	0.0001
Time to chemotherapy initiation	**25.2**	**16.8**	0.58 (0.49, 0.69)	<0.0001
Time to ECOG PS deterioration	12.3	10.9	0.82 (0.71, 0.94)	0.0053
Time to PSA progression	11.1	5.6	0.49 (0.42, 0.57)	<0.0001

Patient Reported Outcomes favored AA + Pr\edn vs. Plac + Predn
Full data to be reported

Note: All secondary end points remain significant after adjusting for multiplicity testing

Data cut off 20/12/2011

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

No New Safety Concerns Identified with Longer AA Treatment than in 301 Study

	AA + Predn (n = 542) %		Plac + Predn (n = 540) %	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Fatigue	39	**2**	34	2
Fluid retention	28	**0.7**	24	1.7
Hypokalemia	17	**2**	13	2
Hypertension	22	**4**	13	3
Cardiac disorders	19	**6**	16	3
Atrial fibrillation	4	**1.3**	5	0.9
ALT increased	12	**5.4**	5	0.8
AST increased	11	**3.0**	5	0.9

Most ALT and AST increases occurred during the first 3 months of treatment

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

Nuovi farmaci in sviluppo

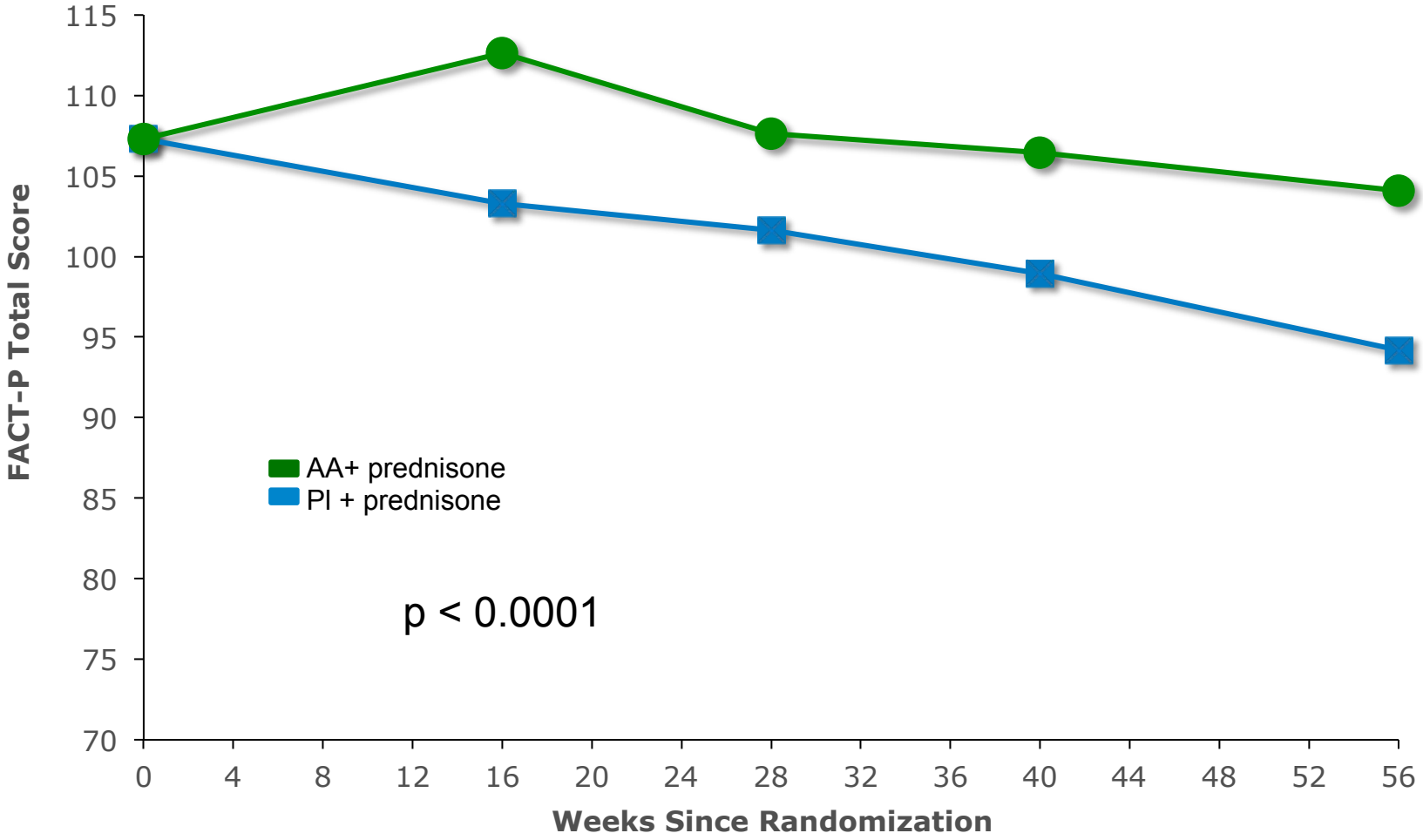
		MoA	NOME
ENDOCRINE- ADT	**MDV3100**	Blocco AR	**Enzalutamide**
	ARN 509	Blocco AR	
	TAK 700	Blocco sintesi Testosterone	**Orteronel**
	TOK 001	Blocco sintesi Testosterone + Blocco AR	**Galeterone**
TARGETED AGENTS		Inibitore Tirosin chinasi, c-MET, VEGFR2	**Cabozantinib**
		Antiangiogenetico	**Tasquinimod**
	OGX 427	Oligonucleotide antisenso anti hsp 27	
	OGX 011	Inibitore clusterina	**Custirsen**
BONE TARGETED	**Prolia o Xgeva**	Mab anti RANKL	**Denosumab**
	Radio 223	Radiofarmaco	**Alpharadin**
Immunoterapia		Vaccino	**Sipuleucel-T**
		Vaccino	**Prostvac**

Conclusioni

Miglioramento delle prospettive per il paziente con Ca della Prostata grazie ai nuovi farmaci:

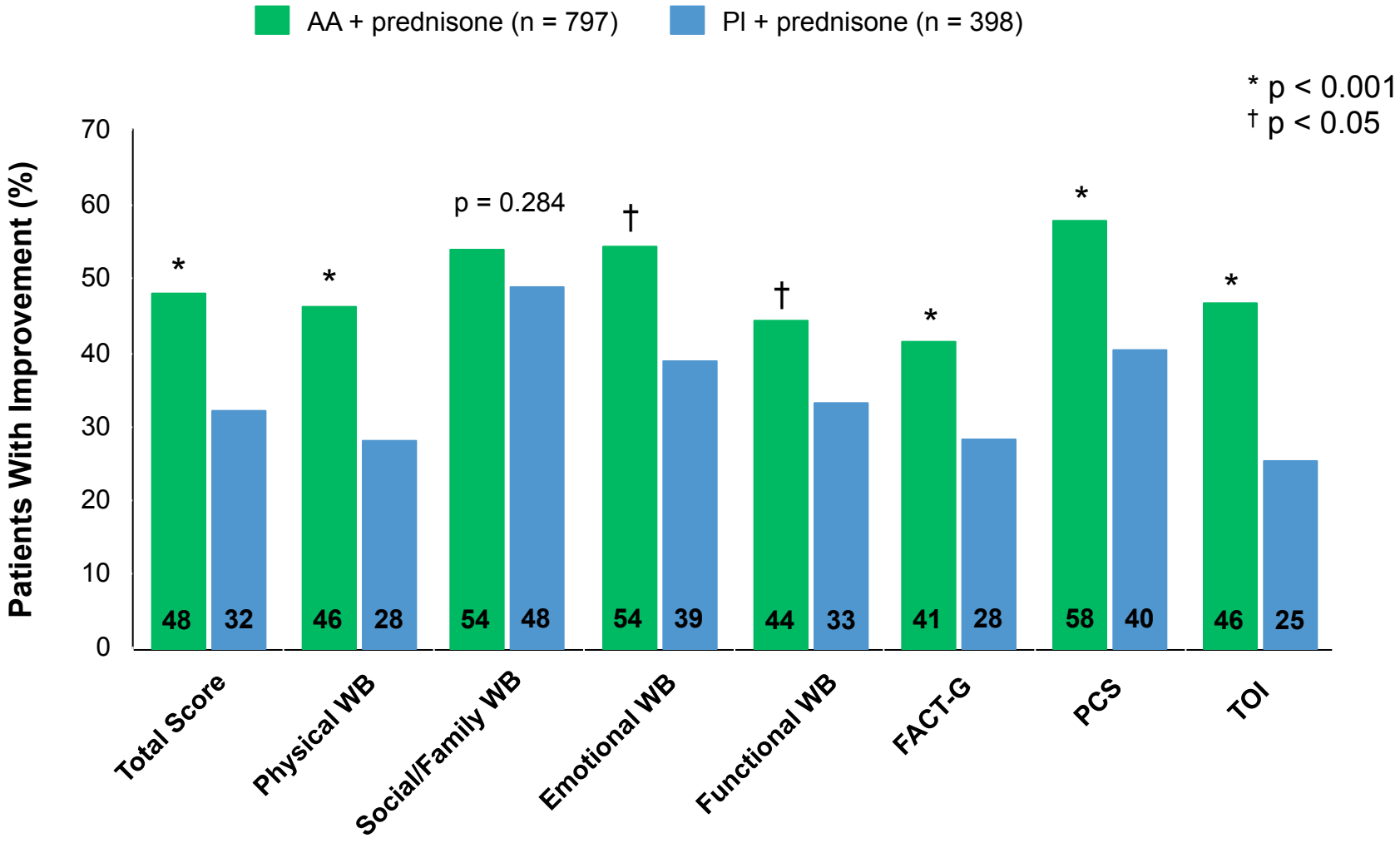
- Miglioramento sopravvivenza
- Riduzione degli eventi scheletrici
- Miglioramento della quality of life

FACT-P: Adjusted Mean Scores Over Time Favour the AA Arm



Harland et al. ECCO 2011: Abstract 7001 (oral presentation)

AA Was Associated With Higher FACT-P Responses



Harland et al. ECCO 2011: Abstract 7001 (oral presentation)