Trattamento della malattia CRPC metastatica (M+)

Terapie ormonali di nuova generazione

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Terapie ormonali di nuova generazione
ABIRATERONE - ENZALUTAMIDE

- Efficacia
- Tossicità
- Sequenze
- Fattori predittivi
- Prospettive future

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Phase III Trials With Life-Prolonging Therapies in Advanced Prostate Cancer

	Study	Agents	N	Indication	HR (95% CI)	ΔOS (mo)
2017	STAMPEDE[1]	ABI/P/SOC vs SOC	1,917	Metastatic hormone-naïve	0.63 (0.52-0.76)	NR
2017	LATITUDE[2]	ABI/P/ADT vs ADT	1,199	Metastatic hormone-naïve	0.62 (0.51-0.76)	NR
2016	STAMPEDE[3]	DOC/SOC vs SOC	1,086	Metastatic hormone-naïve	0.73 (0.59-0.89)	+22.0
2015	CHAARTED[4]	DOC/ADT vs ADT	790	Metastatic hormone-naïve	0.61 (0.47-0.80)	+13.6
2017	PREVAIL[5]	ENZA vs pbo	1,717	mCRPC (pre-DOC) mild/no symptoms , 11% visceral mets	0.71 (0.60-0.84)	+4.0
2012	AFFIRM[6]	ENZA vs pbo (or P)	1,199	mCRPC (post-DOC)	0.63 (0.53-0.75)	+4.8
2015	COU-AA-302[7]	ABI/P vs P	1,088	mCRPC (pre-DOC), mild/no symptoms - No visceral mets	0.81 (0.70-0.93)	+4.4
2012	COU-AA-301[8]	ABI/P vs P	1,195	mCRPC (post-DOC)	0.74 (0.64-0.86)	+4.6
2013	ALSYMPCA[9]	Radium-223 vs pbo	921	mCRPC (post-DOC or unfit for DOC)	0.70 (0.55-0.88)	+2.8
2010	TROPIC[10]	CABA/P vs mito/P	755	mCRPC (post-DOC)	0.70 (0.59-0.83)	+2.4
2010	IMPACT[11]	Sipuleucel-T vs pbo	512	mCRPC (pre-DOC) mild/no symptoms - No visceral mets	0.78 (0.61-0.98)	+4.1
2004	TAX-327[12]	DOC/P vs mito/P	1,006	mCRPC, symptomatic or not	0.76 (0.62-0.94)	+2.9

ABI, abiraterone; ADT, androgen deprivation therapy; CABA, cabazitaxel; DOC, docetaxel; ENZA, enzalutamide; mCRPC, metastatic castration resistant prostate cancer; mito, mitoxantrone; P, prednisone; Pbo, placebo; SOC, standard of care.

1. James ND et al. N Engl J Med. 2017 Jun 3. doi: 10.1056/NEJMoa1702900 2. Fizazi K, et al. *N Engl J Med.* 2017;377:352-360; 3. James ND. *Lancet*. 2016;387:1163–77; 4. Sweeney CJ. *N Engl J Med*. 2015;373:737–46; 5. Beer TM. *Eur Urol.* 2017 Feb;71(2):151–54; 6. Scher HI. *NEJM*. 2012;367:1187–97; 7. Ryan C. *Lancet Oncol*. 2015;16:152–60; 8. Fizazi K. *Lancet Oncol.* 2012;13:983–92; 9. Parker C et al. *NEJM*. 2013;369:213–23; 10. de Bono JS. *Lancet*. 2010;376:1147–54; 11. Kantoff PW. *NEJM*. 2010;363:411–22; 12. Tannock IF. *NEJM*. 2004;351:1502–12.

POST CHEMIO

COU-AA-301

- 1195 patients with progressive, mCRPC
- Failed 1 or 2 chemotherapy regimens, one of which contained docetaxel
- Randomised 2:1
- Stratification by:
  - ECOG performance status (0-1 vs. 2)
  - Worst pain over previous 24 hours (BPI short form; 0-3 [absent] vs. 4-10 [present])
  - Prior chemotherapy (1 vs. 2)
  - Type of progression (PSA only vs. radiographic progression with or without PSA progression)

Abiraterone acetate 1000 mg daily

Prednisone 5mg twice daily

Placebo daily

Prednisone 5mg twice daily

Efficacy end points

Primary end point:
- OS

Secondary end points:
- PSA response
- rPFS

Additional end points:
- Pain
- SREs

AFFIRM

Patient Population

1199 patients with progressive CRPC

*Failed docetaxel chemotherapy

Randomised 2:1

Enzalutamide 160mg daily (n=800)

Placebo (n=399)

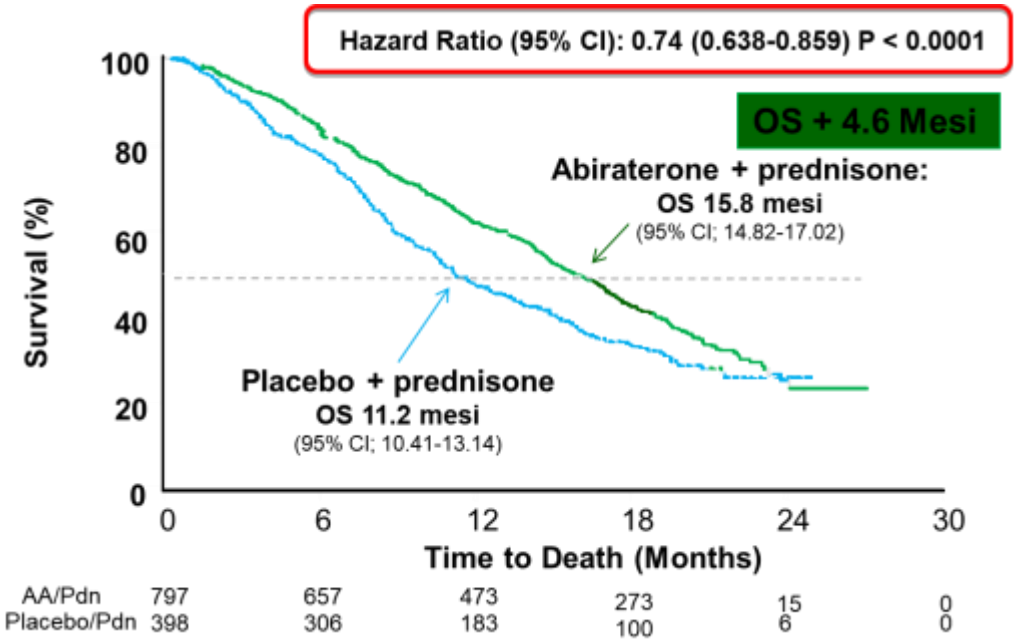
Primary Endpoint:
- OS

Secondary end points:
- PSA response
- OR
- rPFS
- TTPP
- Time to First SRE
- Quality of Life

Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study

Karim Fizazi, Howard I Scher, Arturo Molina, Christopher J Logothetis, Kim N Chi, Robert J Jones, John N Staffurth, Scott North, Nicholas J Vogelzang, Fred Saad, Paul Mainwaring, Stephen Harland, Oscar B Goodman Jr, Cora N Sternberg, Jin Hui Li, Thian Kheoh, Christopher M Haqq, Johann S de Bono, for the COU-AA-301 Investigators*

COU-AA-301

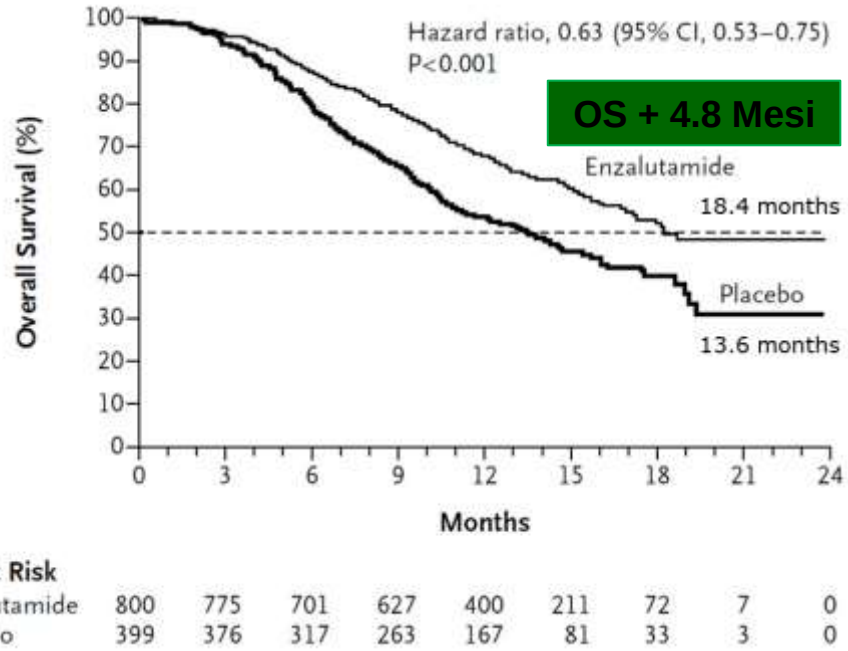


Fizazi, Lancet Oncology 2012

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*

AFFIRM

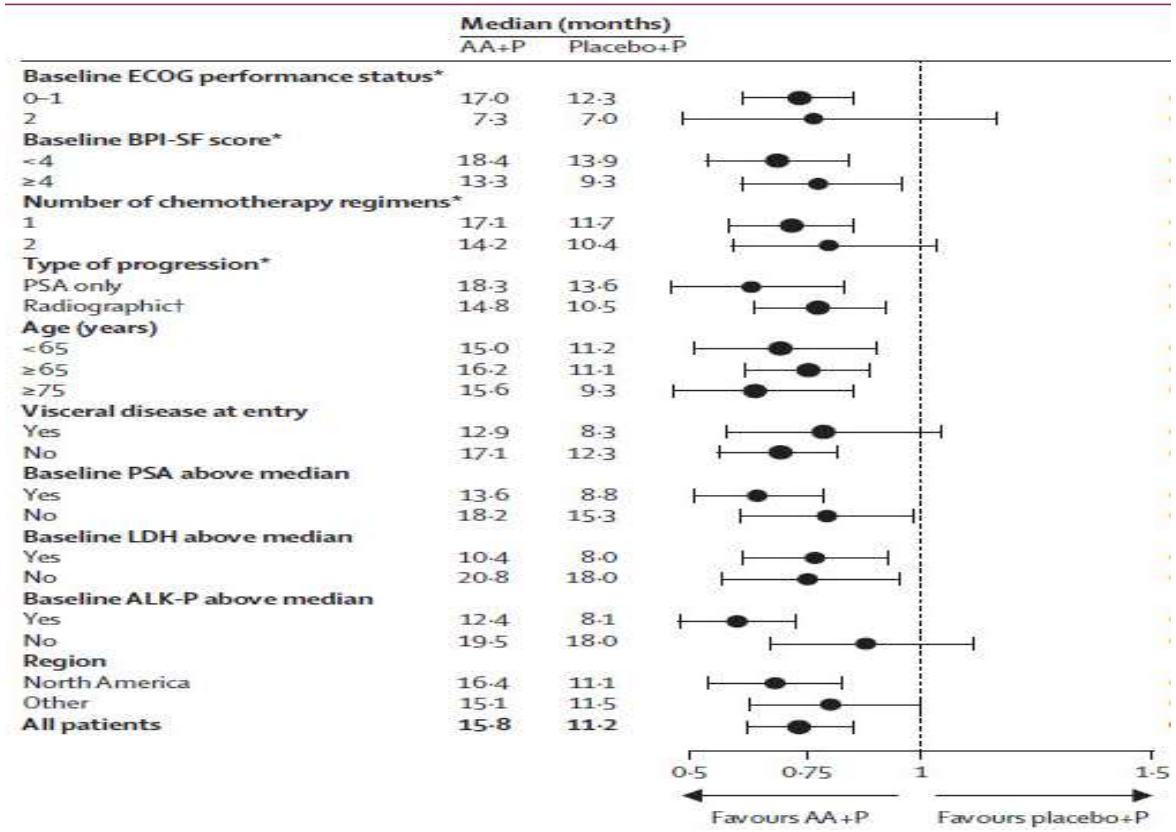


Scher H et al. N Engl J Med 2012; 367(13):1187-97

Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study

*Karim Fizazi, Howard I Scher, Arturo Molina, Christopher J Logothetis, Kim N Chi, Robert J Jones, John N Staffurth, Scott North, Nicholas J Vogelzang, Fred Saad, Paul Mainwaring, Stephen Harland, Oscar B Goodman Jr, Cora N Sternberg, Jin Hui Li, Thian Kheoh, Christopher M Haqq, Johann S de Bono, for the COU-AA-301 Investigators**

COU-AA-301

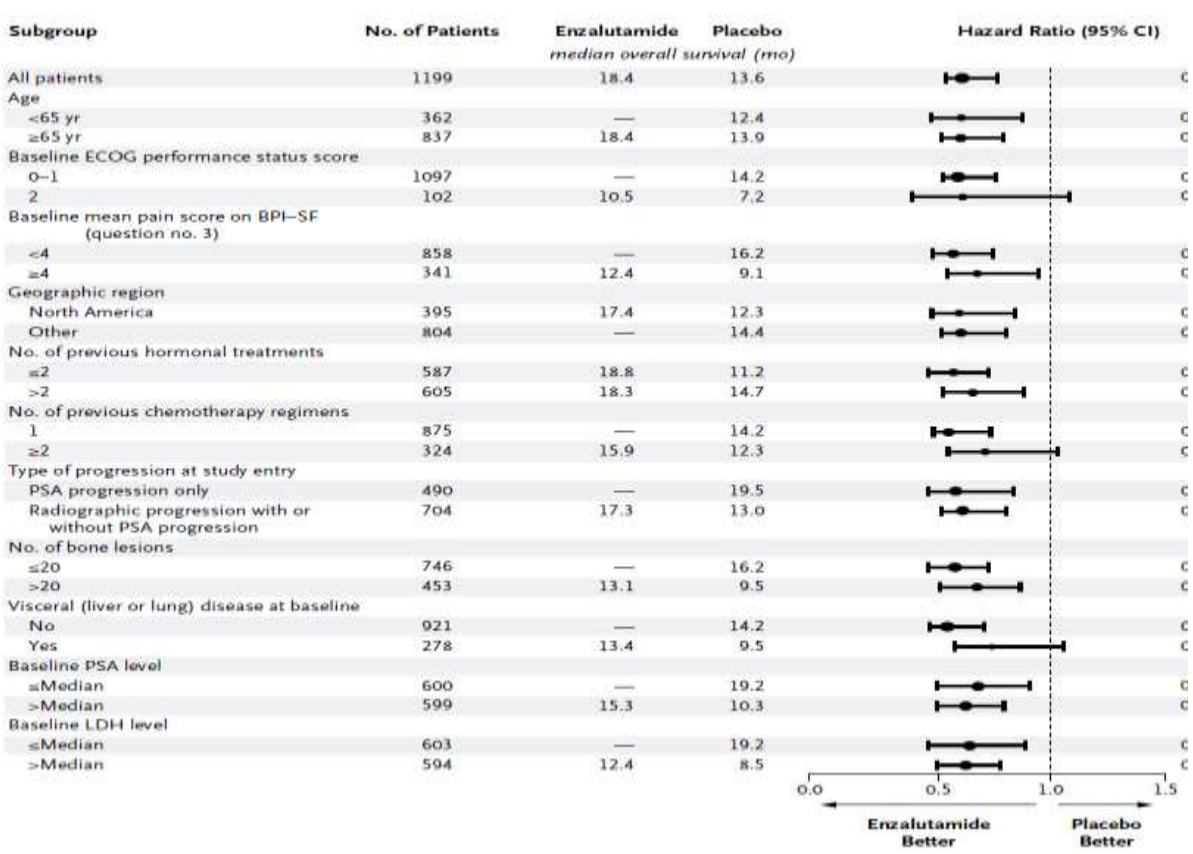


Fizazi et al. Lancet Oncol 2012; 13(10): 983-992

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*

AFFIRM



Scher H et al. N Engl J Med 2012; 367(13):1187-97

Metastasi Viscerali

COU-AA-301

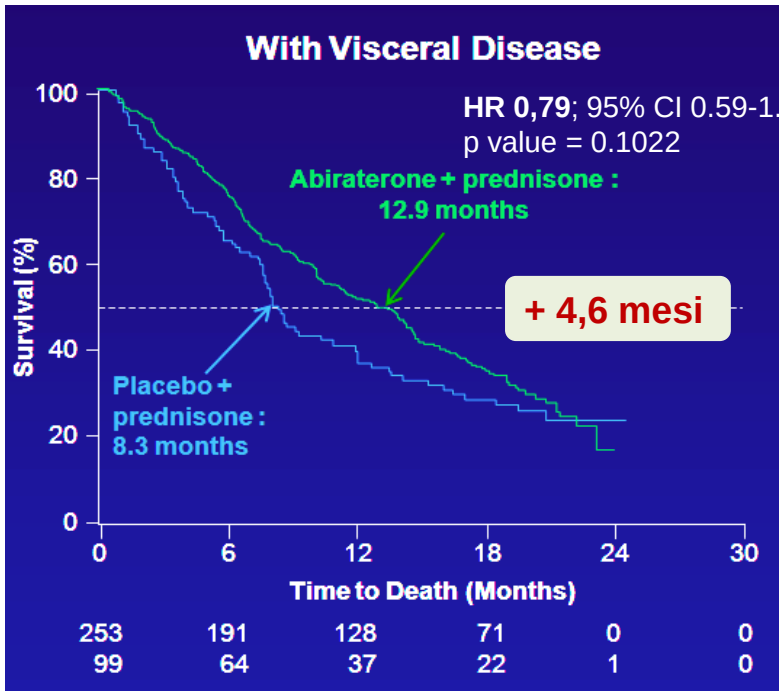
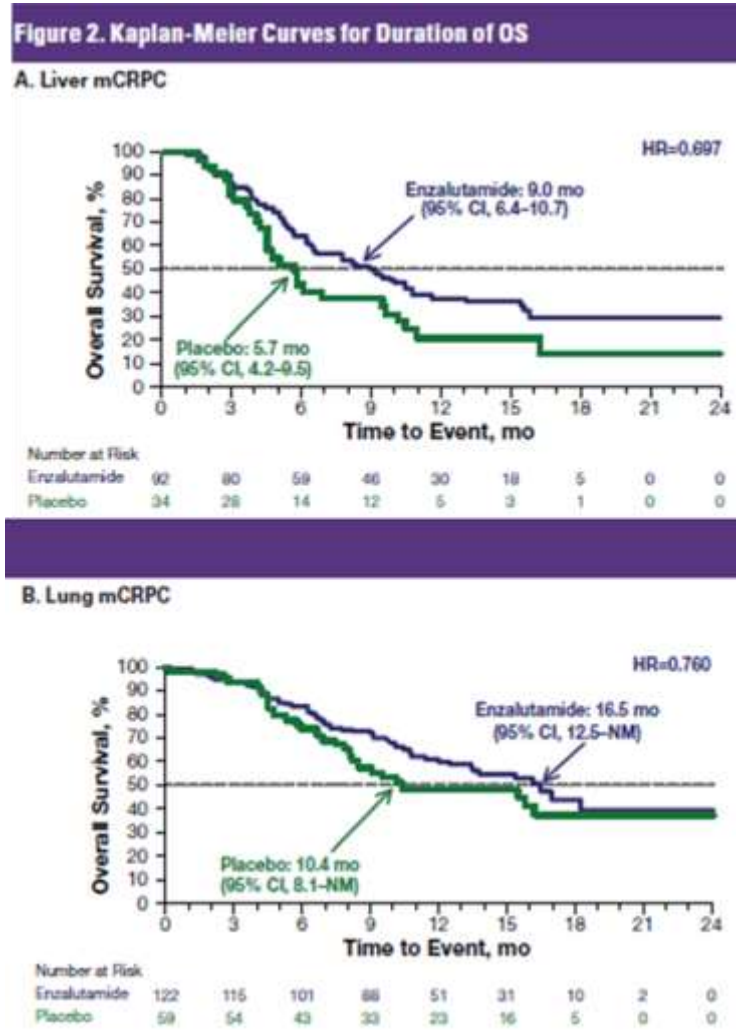


Table 3. Outcomes in patients with visceral disease by site

Outcome	AA + P		P
Lung metastases	(*n* = 105)		(*n* = 45)
Median OS, months	13.9	12.0	7.9
Median rPFS, months	5.6	3.8	2.8
PSA response rate, %	28.6		6.7
Liver metastases	(*n* = 89)		(*n* = 29)
Median OS, months	7.3	6.7	4.0
Median rPFS, months	2.8	2.8	2.8
PSA response rate, %	13.5		3.5
Measurable disease[a]			
Lung metastases	(*n* = 74)		(*n* = 27)
ORR, %	12.2		0
Liver metastases	(*n* = 73)		(*n* = 23)
ORR, %	4.1		0

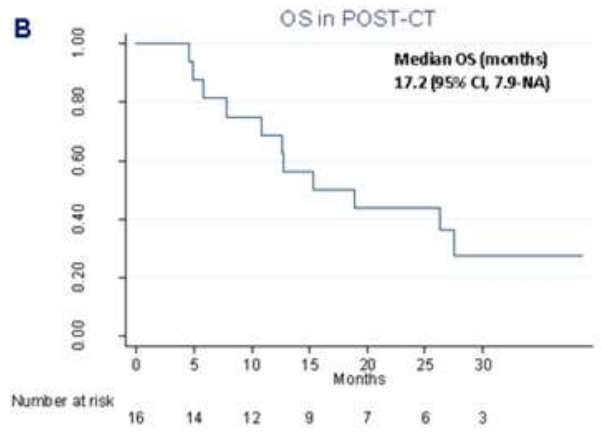
Goodman et al, *Prostate Cancer and Prostatic Disease* 2013

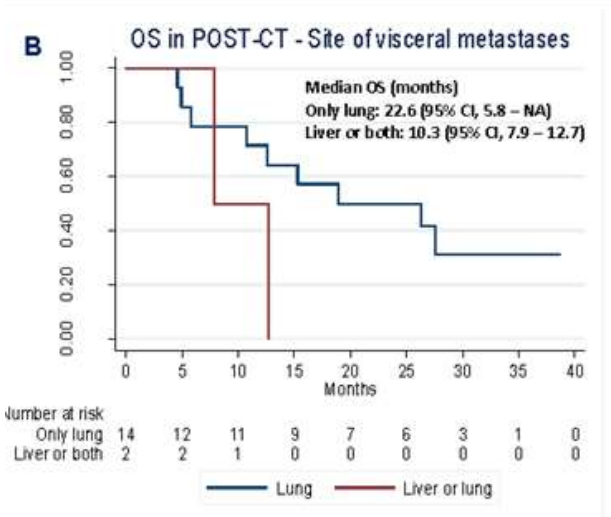
AFFIRM



Loriot Y et al. ASCO 2013; Abstract 5065

Abiraterone acetate treatment in castration-resistant prostate cancer patients with visceral metastases: a real-world experience.





Facchini G. et al. *Anticancer Drugs* 2018 in press

All Secondary End Points Achieved Statistical Significance

COU-AA-301

	Abiraterone + Prednisone (n = 797)	Placebo + Prednisone (n = 398)	HR 95% CI	P Value
TTPP (months)	10.2	6.6	0.58 (0.46, 0.73)	< 0.001
rPFS (months)	5.6	3.6	0.67 (0.58, 0.78)	< 0.001
PSA response rate				
Total	38.0%	10.1%	-	< 0.001
Confirmed	29.1%	5.5%	-	< 0.001
Objective response (RECIST)	14.0%	2.8%	-	< 0.001

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

AFFIRM

Response	Enzalutamide (N=800)	Placebo (N=399)	P Value
PSA Response	n=731	n=330	
Decline ≥50% from baseline	54%	2%	<0.001
Decline ≥90% from baseline	25%	1%	<0.001
Soft tissue objective response	n=446	n=208	
CR or PR	29%	4%	<0.001
FACT-P quality of life response	n=651	n=257	
Quality of life response	43%	18%	<0.001
Median time to first skeletal related event	16.7 months	13.3 months	<0.001

Scher H et al. N Engl J Med 2012; 367(13):1187-97

Abiraterone acetate for patients with metastatic castration-resistant prostate cancer progressing after chemotherapy: final analysis of a multicentre, open-label, early-access protocol trial

*Cora N Sternberg, Daniel Castellano, Gedske Daugaard, Lajos Géczi, Sebastien J Hotte, Paul N Mainwaring, Fred Saad, Ciro Souza, Miah H Tay, José M Tello Garrido, Luca Galli, Anil Londhe, Peter De Porre, Betty Goon, Emma Lee, Tracy McGowan, Vahid Naini, Mary B Todd, Arturo Molina, Daniel J George, for the Abiraterone Global EAP Investigators**

Real World

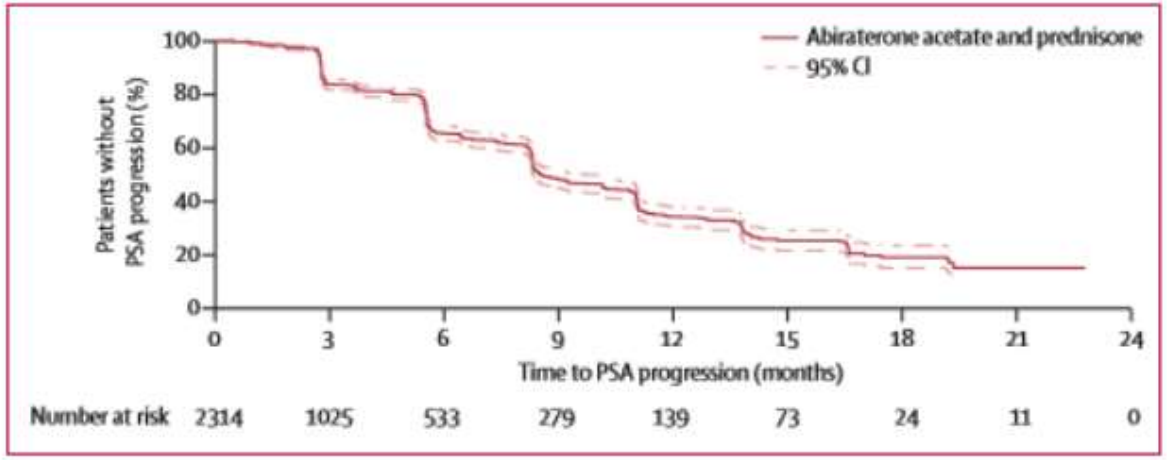


Figure 1: **Time to PSA progression**
PSA=prostate-specific antigen.

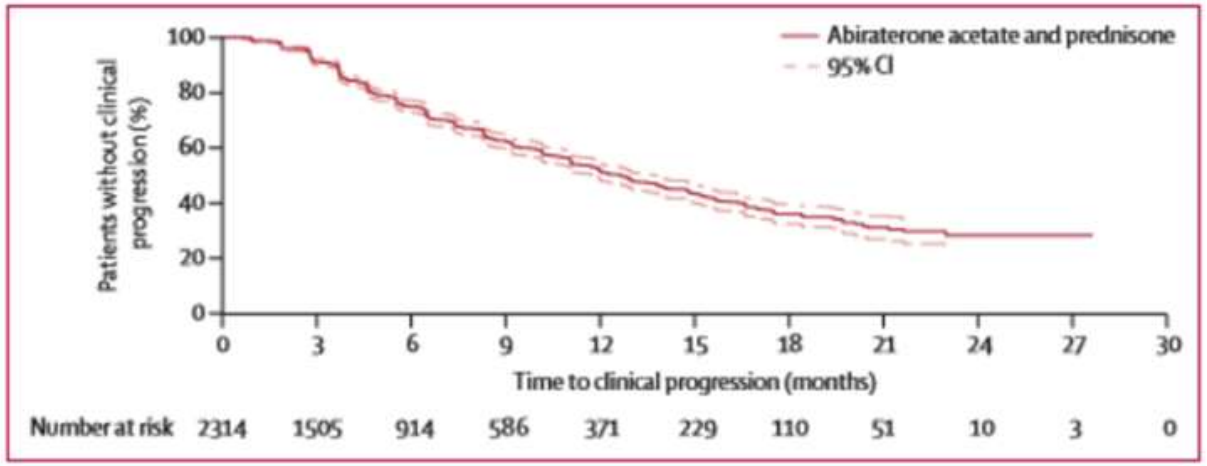


Figure 2: **Time to clinical progression**

Sternberg CN et al. Lancet Oncol 2014; 15: 1263–68

Enzalutamide after chemotherapy in advanced castration-resistant prostate cancer: the Italian Named Patient Program

Francesca Maines*[,1], Ugo De Giorgi[2], Giuseppe Procopio[3], Gaetano Facchini[4], Lucia Fratino[5], Roberto Sabbatini[6], Donatello Gasparro[7], Umberto Basso[8], Claudia Mosillo[9], Enrico Campadelli[10], Francesco Massari[11], Teodoro Sava[12], Suzana Sirotova[13], Caterina Messina[14], Sarah Scagliarini[15], Vincenza Conteduca[2], Elena Verzoni[3], Sabrina Rossetti[4], Antonello Veccia[1], Stefania Kinspergher[1] & Orazio Caffo[1]

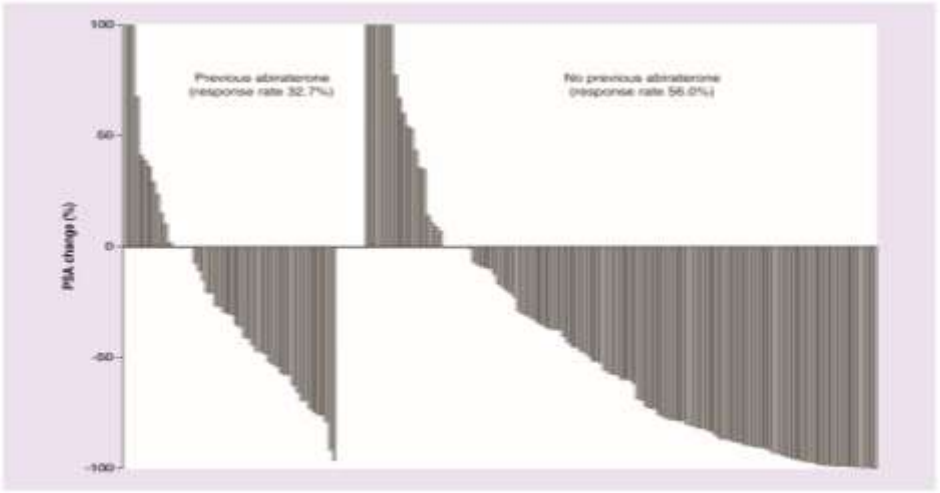


Figure 1. Best prostate-specific antigen response to enzalutamide treatment.
PSA: Prostate-specific antigen.

Summary points

- We collected data on 209 patients who had received enzalutamide in the Italian Named Patient Program and experienced disease progression during or after docetaxel..
- Our population significantly differed from that enrolled in the pivotal trial in terms of percentage of patients aged ≥75 years (42.6 vs 24.9%; p < 0.0001), patients with pain (42.1 vs 28.3%; p = 0.0002), patients with Eastern Cooperative Oncology Group performance status 2 (14.4 vs 8.8%; p = 0.01); moreover, our patients had a significantly higher rate of GS ≥8 (59.8 vs 45.8%; p = 0.0002). Finally, 42.1% of the patients received enzalutamide after taking at least another new agent (abiraterone, or cabazitaxel, or both) after the docetaxel first-line treatment.
- An overall reduction in prostate-specific antigen of at least 50% in comparison with baseline was observed in 49.1% of the patients, but a clear difference was observed according to the previous exposure to abiraterone: patients who had been previously treated with the drug achieved a biochemical response in 32.7% of cases, compared with 56% of the patients who did not receive it (p = 0.005).
- Despite the worse clinical features of our population, our analysis confirms the good safety profile of the drug, with a low incidence of serious or high-grade adverse events.

Real World

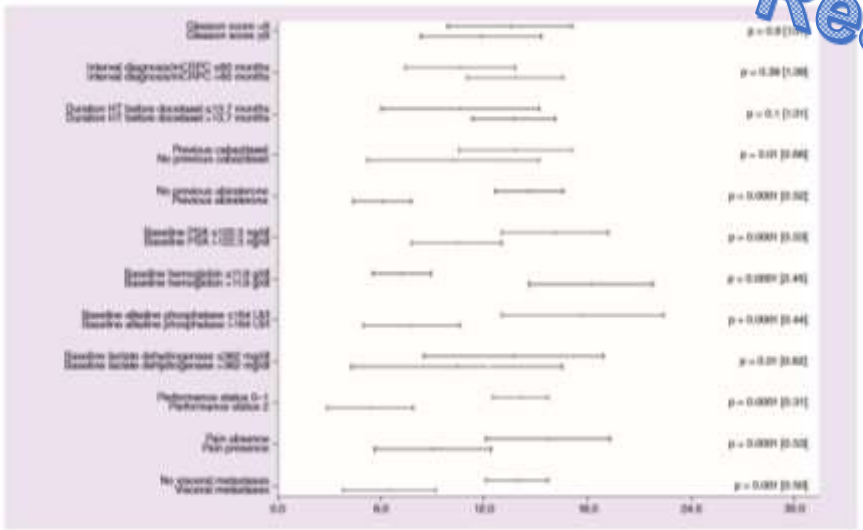


Figure 3. Overall survival by selected factors. The number of patients in each group is shown in brackets: the central dot indicates the median value and the lines the 95% CI. The p-values were calculated using the cox regression analysis, with hazard ratios indicated in square brackets.
mCRPC: Metastatic castration-resistant prostate cancer; PSA: Prostate-specific antigen.

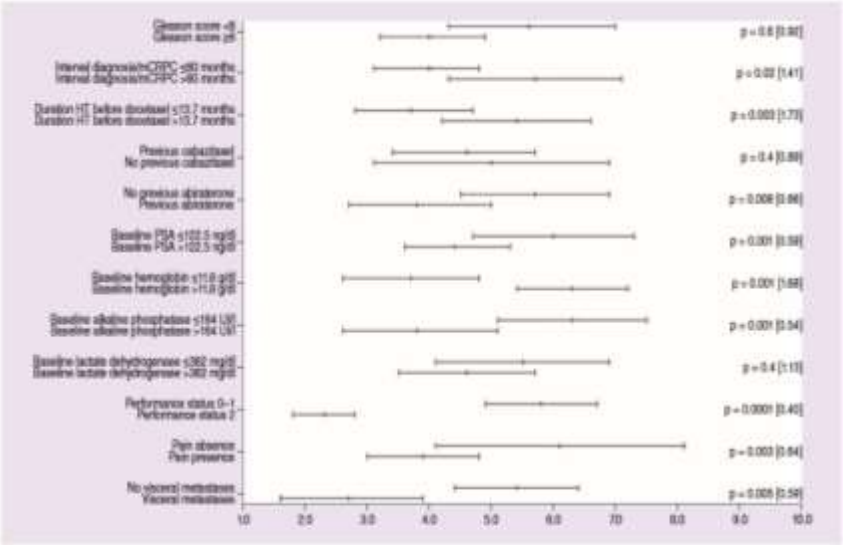
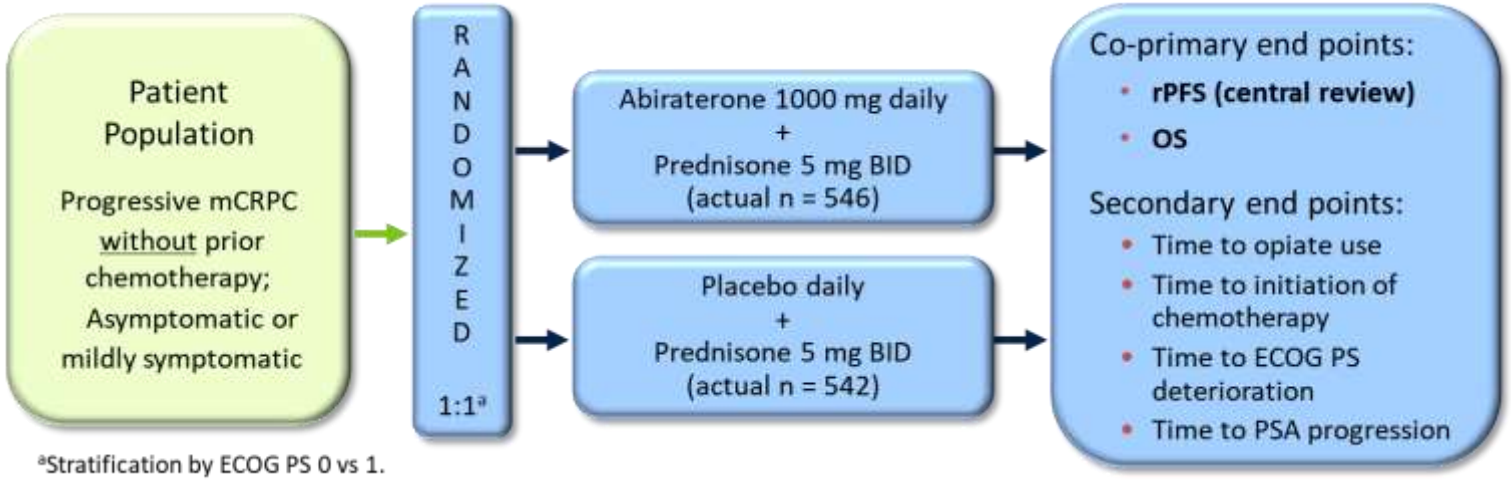


Figure 2. Progression-free survival by selected factors. The number of patients in each group is shown in brackets: the central dot indicates the median value and the lines the 95% CI. The p-values were calculated using the cox regression analysis, with hazard ratios indicated in square brackets.
mCRPC: Metastatic castration-resistant prostate cancer; PSA: Prostate-specific antigen.

Maines F. et al. FutureOncol. 10.2217/fon-2018-0113C 2018

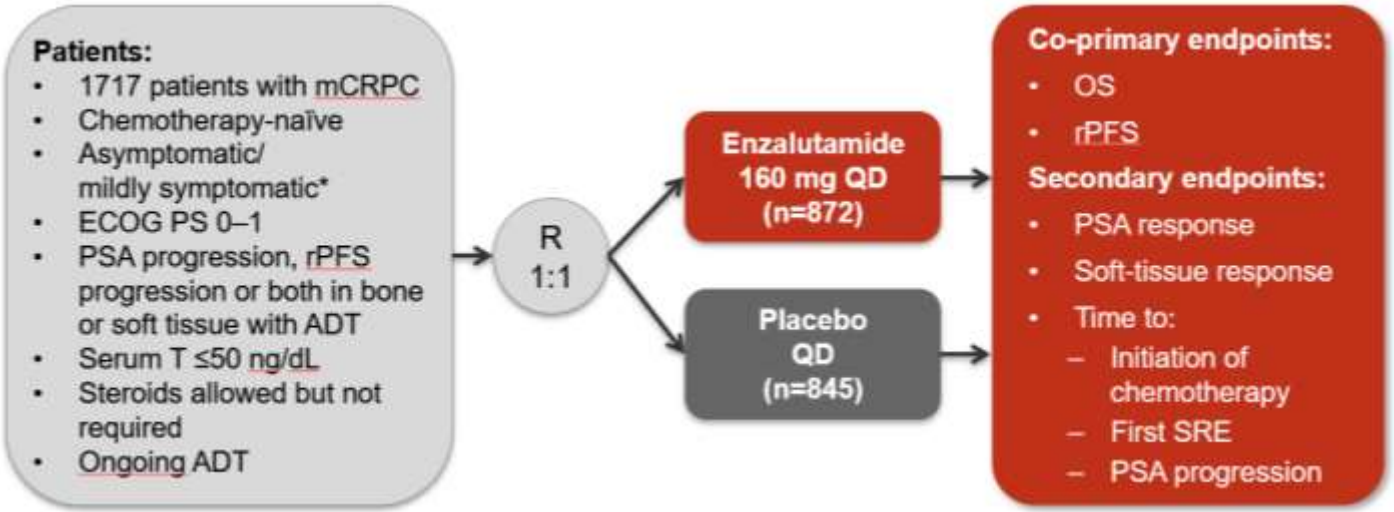
POST ADT

COU-AA-302



[a]Stratification by ECOG PS 0 vs 1.

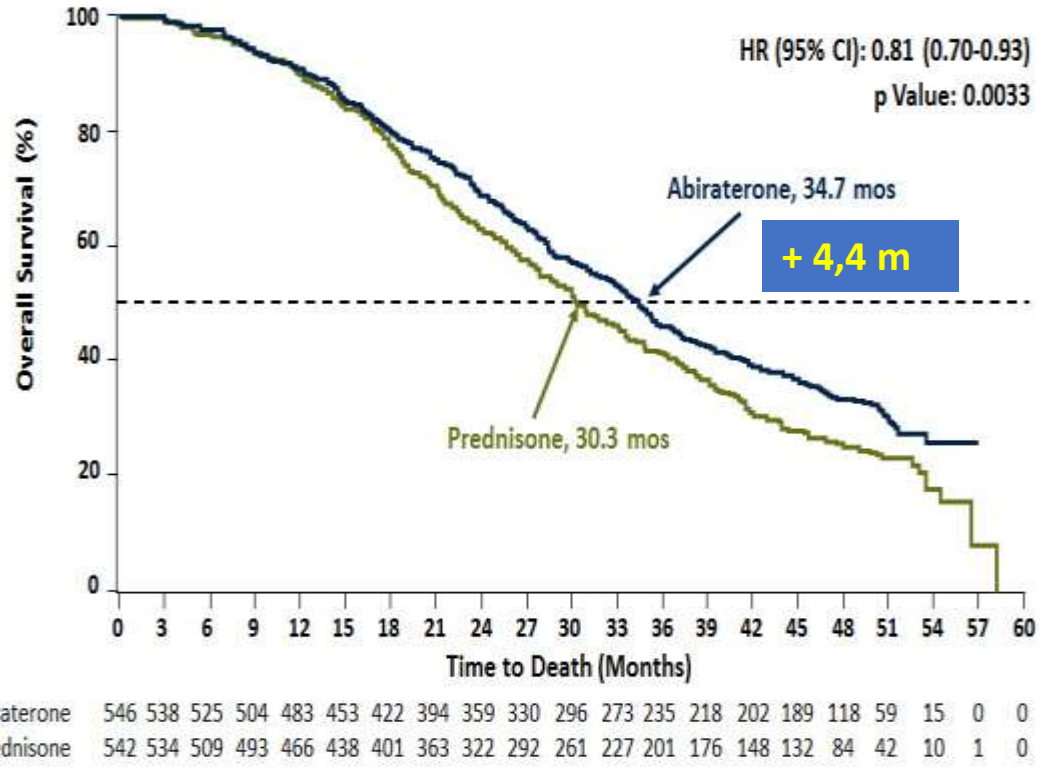
PREVAIL

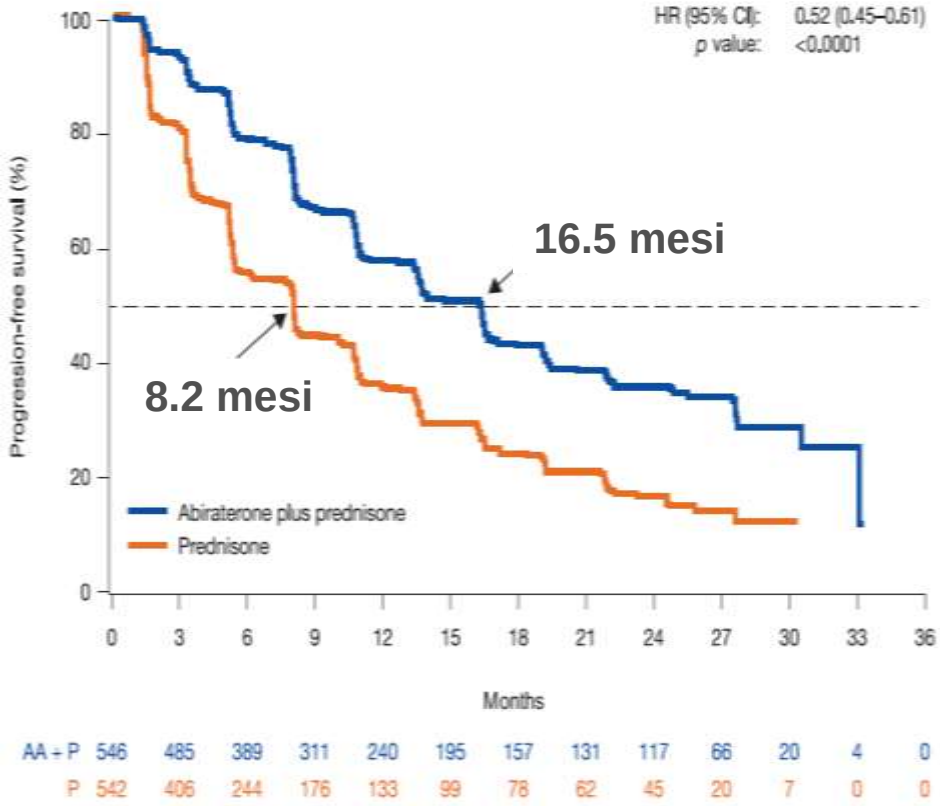


Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study

Charles J Ryan, Matthew R Smith, Karim Fizazi, Fred Saad, Peter F A Mulders, Cora N Sternberg, Kurt Miller, Christopher J Logothetis, Neal D Shore, Eric J Small, Joan Carles, Thomas W Flaig, Mary-Ellen Taplin, Celestia S Higano, Paul de Souza, Johann S de Bono, Thomas W Griffin, Peter De Porre, Margaret K Yu, Youn C Park, Jinhui Li, Thian Kheoh, Vahid Naini, Arturo Molina, Dana E Rathkopf, for the COU-AA-302 Investigators*

COU-AA-302





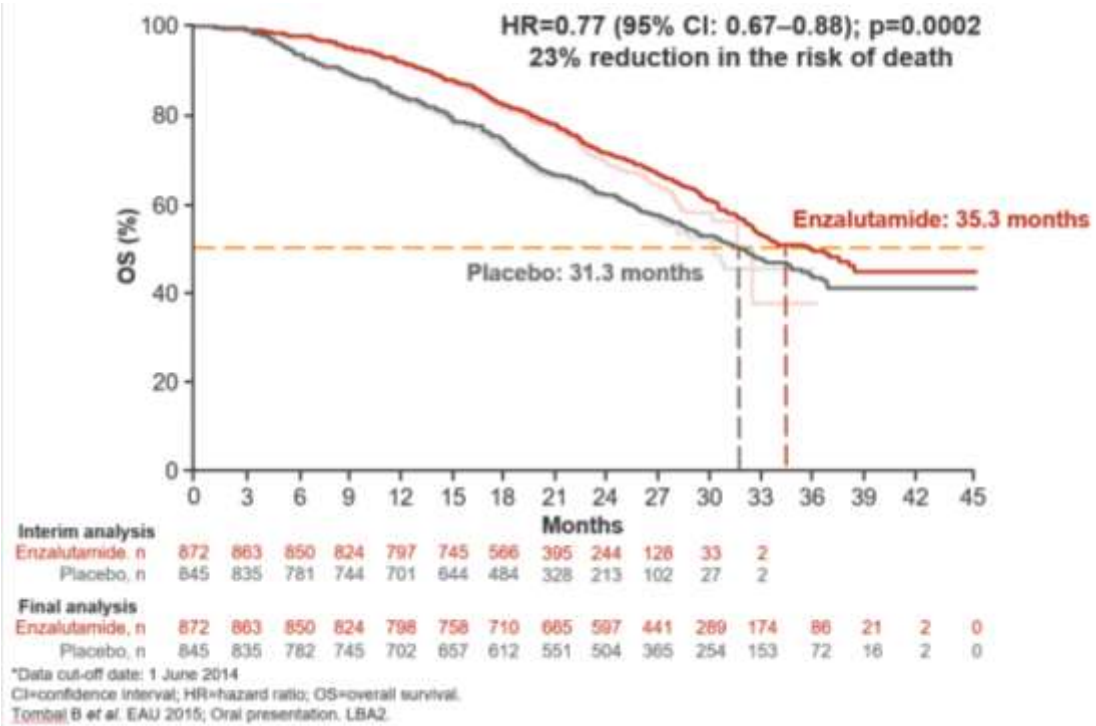
Ryan C et al. Lancet Oncology 2015

1. *Rathkopf et al, European Urology 2014*

Enzalutamide in Metastatic Prostate Cancer before Chemotherapy

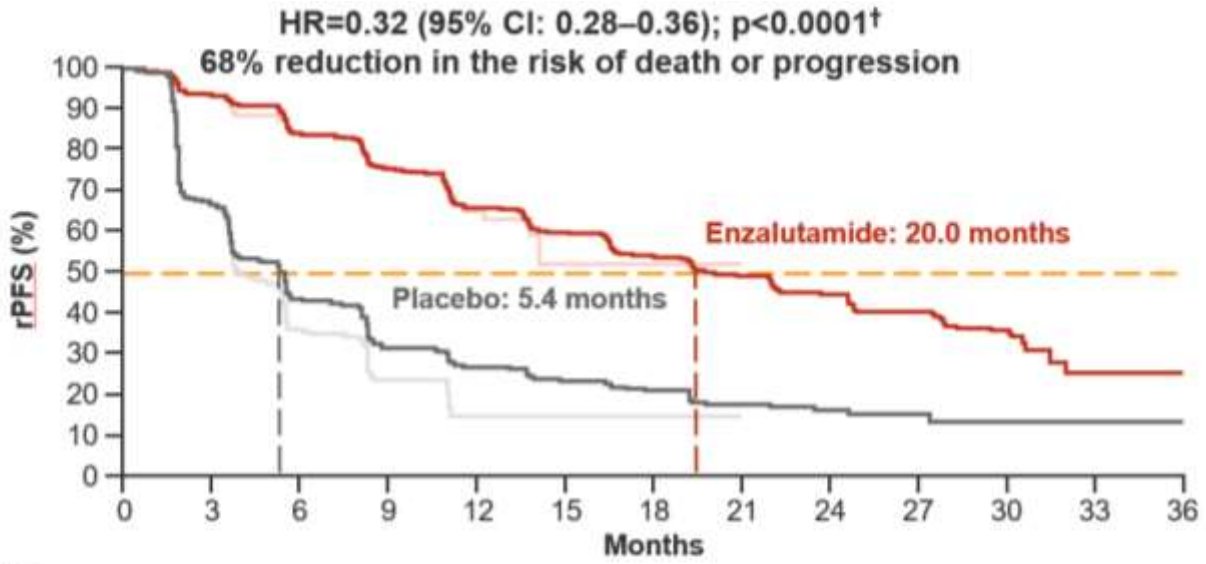
T.M. Beer, A.J. Armstrong, D.E. Rathkopf, Y. Loriot, C.N. Sternberg, C.S. Higano, P. Iversen, S. Bhattacharya, J. Carles, S. Chowdhury, I.D. Davis, J.S. de Bono, C.P. Evans, K. Fizazi, A.M. Joshua, C.-S. Kim, G. Kimura, P. Mainwaring, H. Mansbach, K. Miller, S.B. Noonberg, F. Perabo, D. Phung, F. Saad, H.I. Scher, M.-E. Taplin, P.M. Venner, and B. Tombal, for the PREVAIL Investigators*

PREVAIL



Interim analysis																	
Enzalutamide, n	872	863	850	824	797	745	566	395	244	126	33	2					
Placebo, n	845	835	781	744	701	644	484	328	213	102	27	2					
Final analysis																	
Enzalutamide, n	872	863	850	824	798	758	710	665	597	441	289	174	86	21	2	0	
Placebo, n	845	835	782	745	702	657	612	551	504	365	254	153	72	16	2	0	

*Data cut-off date: 1 June 2014
CI=confidence interval; HR=hazard ratio; OS=overall survival.
Tombal B *et al.* EAU 2015; Oral presentation. LBA2.



Final analysis													
Enzalutamide, n	832	514	256	128	34	5	1	0					
Placebo, n	801	305	79	20	5	0	0	0					
Extended analysis													
Enzalutamide, n	872	784	666	572	472	398	326	231	155	93	53	7	0
Placebo, n	845	463	239	150	105	83	60	31	18	9	3	0	0

*Date of analysis: 15 January 2014. †p value not type I error adjusted or corrected.
CI=confidence interval; HR=hazard ratio; NYR=not yet reached; rPFS=radiograohic progression-free survival.
Beer TM, *et al.* ASCO 2015; Poster presentation. Abstract 5036.

Beer TM, *et al.* N Engl J Med 2014;371:424-33.

COU-AA-302: Efficacia su tutti gli endpoints secondari

Ritarda significativamente il **dolore** del 45%
Ritarda la comparsa di **SREs** di quasi 5 mesi

Logothetis et al. Lancet Oncol 2012

Efficace in pazienti con **Metastasi viscerali**

Goodman O et al. J Clin Oncol 2012

Efficace e sicuro anche in **pazienti anzianI**

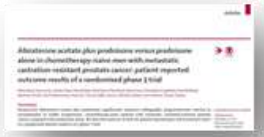
Mulders et al. Eur Urol 2013

Migliora la **qualità della vita**

Harland et al. Eur J Cancer 2013

Migliora in modo rapido e significativo la **fatigue**

Sternberg et al Ann Oncol 2013



Ritarda lo sviluppo e la progressione del **dolore** di quasi 8 mesi

Basch et al. Lancet Oncol 2013

Efficace e sicuro anche nei **pazienti anziani**
Smith et al J Uro 2015

L'uso concomitante di Abi con una **BTT** è associata ad un ritardo della progressione della malattia

Saad et al Eurology 2015

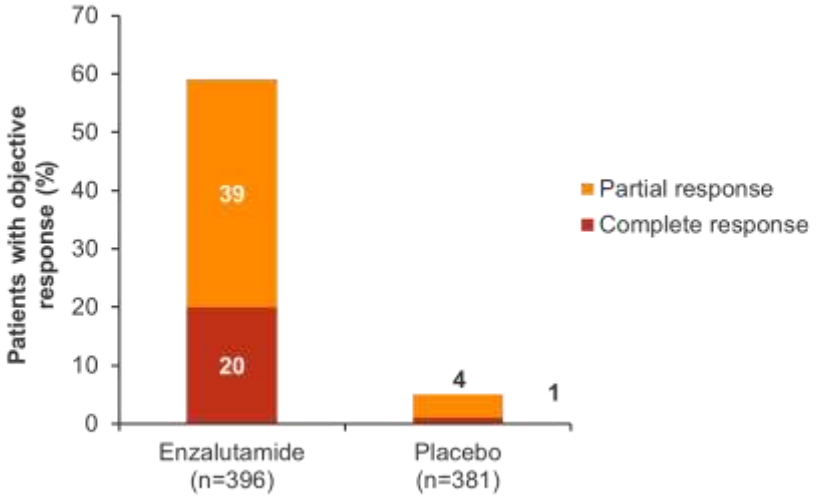
Abi è efficacie indipendentemente dall'esposizione ad una **terapia endocrina precedente**

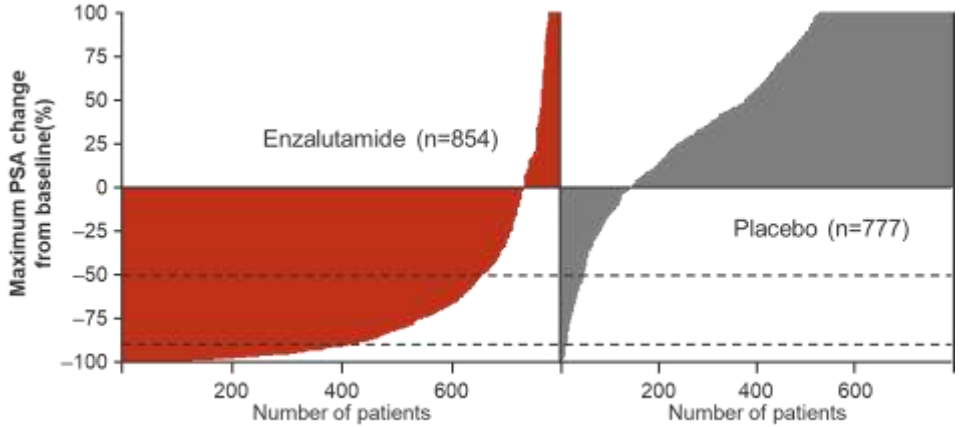
Bellmunt J et al. Eur Urology 2015

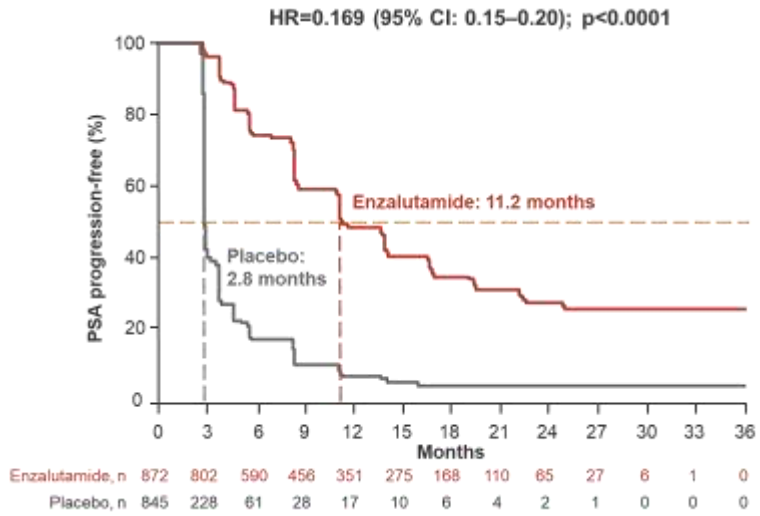
I pazienti **asintomatici, con PSA <80 ng/mL e Gleason score <8** traggono maggior beneficio dal trattamento con Abi

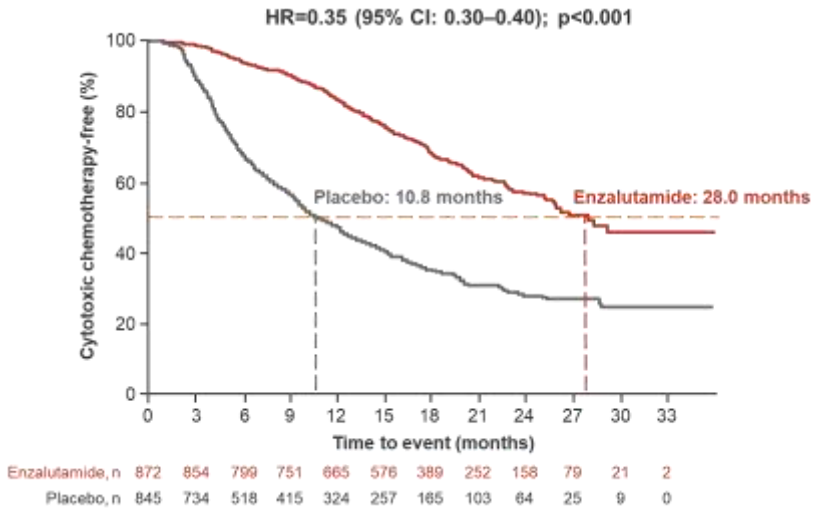
Miller k et al. European urology 2017

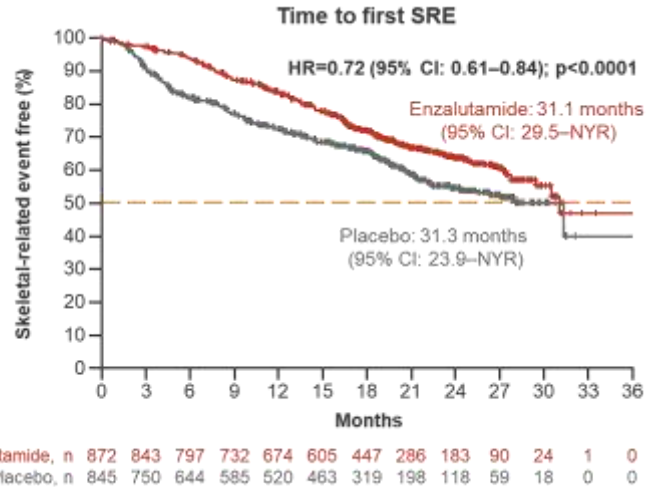
PREVAIL: Efficacia su tutti gli endpoints secondari





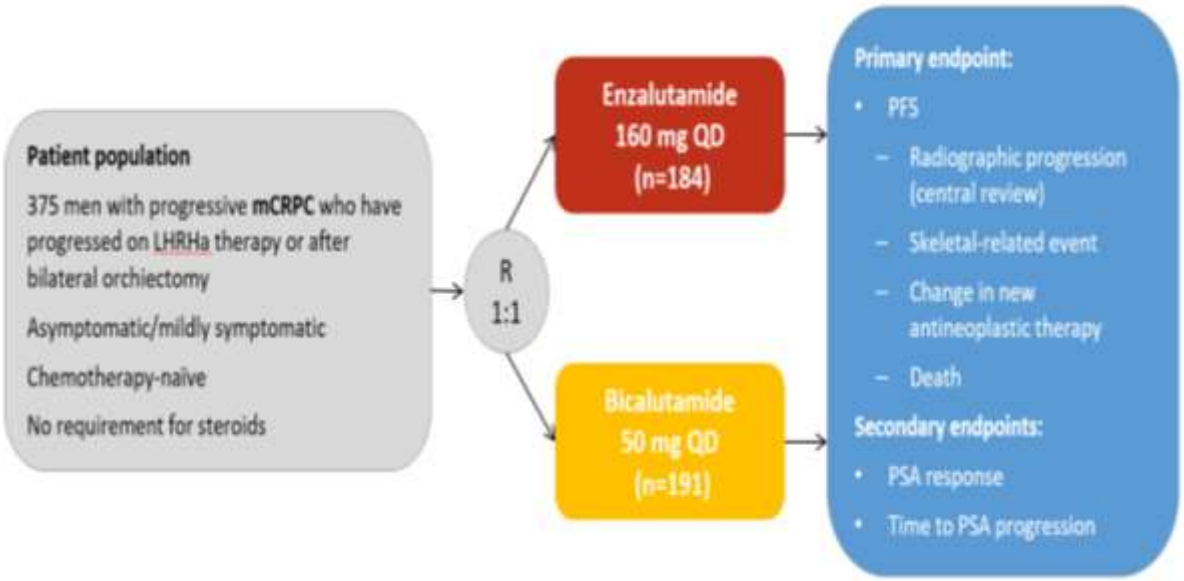




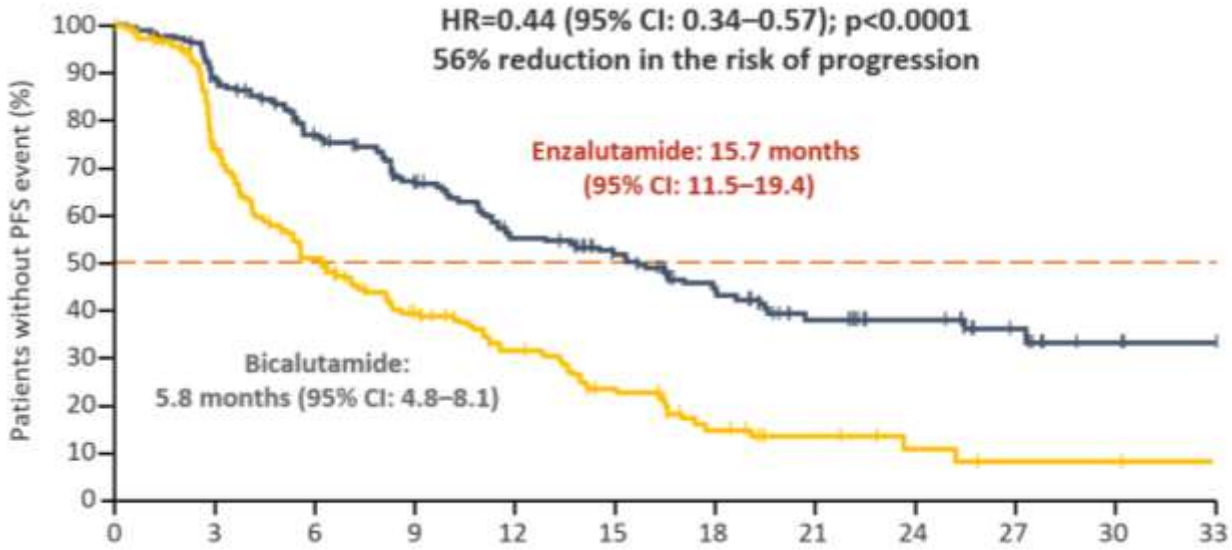


Beer TM, *et al.* N Engl J Med 2014;371:424-33.

TERRAIN



Progression-free survival



LHRHa=luteinizing hormone-releasing hormone analogue; mCRPC=metastatic castration-resistant prostate cancer; PFS=progression-free survival; PSA=prostate-specific antigen; QD=once daily; R=randomised.
Heidenreich A, *et al.* EAU 2015; Oral presentation LBA3.

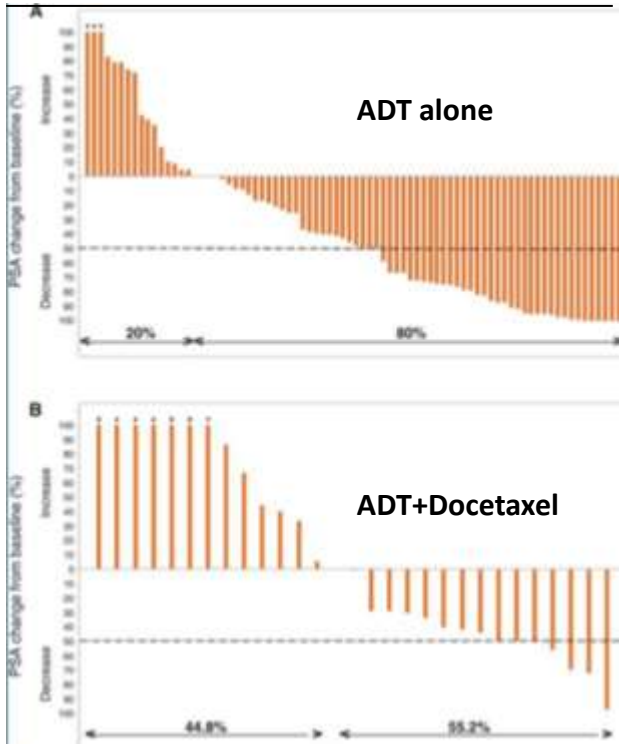
Shore, Neal D et al., The Lancet Oncology , 2016 Volume 17 , Issue 2 , 153 – 163

mCRPC POST CHAARTED

mCRPC POST CHAARTED

- No prospective data exist
- Small and few retrospective studies
- Data on sequencing from a retrospective follow up of men on the GETUG AFU-15 trial (ADT vs ADT+Docetaxel in mHSPC)

Docetaxel PSA response



First line agent in the mCRPC setting	PSA ≥ 50%		PSA PFS	
	ADT alone in mHSPC setting	ADT+ Docetaxel in mHSPC setting	ADT alone in mHSPC setting	ADT+ Docetaxel in mHSPC setting
Docetaxel	38% (25/66)	20% (4/20)	6 months	4.1 months
Bicalutamide	43% (12/28)	17% (4/23)	5.1 months	3.2 months
Abiraterone or Enzalutamide	83% (5/6)	52% (10/19)	N/A	N/A

Lavaud et al. *Eur Urol* 2018; 73(5):696-703

Terapie ormonali di nuova generazione
ABIRATERONE - ENZALUTAMIDE

- Efficacia
- **Tossicità**
- Sequenze
- Fattori predittivi
- Prospettive future

AEs of Special Interest

COU-AA-301

	Abiraterone + Prednisone (n = 791)			Placebo + Prednisone (n = 394)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Fluid retention and edema	31%	2%	<1%	22%	1%	0
Hypokalemia	17%	3%	<1%	8%	1%	0
Cardiac disorders	13%	3%	1%	11%	2%	<1%
LFT abnormalities	10%	3%	<1%	8%	3%	<1%
Hypertension	10%	1%	0	8%	<1%	0

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

AFFIRM

	All Grades		Grade ≥3	
	Enzalutamide (n=800)	Placebo (n=399)	Enzalutamide (n=800)	Placebo (n=399)
Fatigue	34%	29%	6%	7%
Diarrhoea	21%	18%	1%	<1%
Hot flash	20%	10%	0	0
Musculoskeletal pain	14%	10%	1%	<1%
Headache	12%	6%	<1%	0
Clinically significant AEs				
Cardiac disorders				
Any	6%	8%	1%	2%
Myocardial infarction	<1%	<1%	<1%	<1%
LFT abnormalities**	1%	2%	<1%	<1%
Seizure	<1% (5)	0	<1% (5)	0

Scher H et al. N Engl J Med 2012; 367(13):1187-97

I dati di safety al follow-up di 4 anni confermano il profilo di sicurezza favorevole di Abiraterone nel paz mCRPC

COU-AA-302 (final analysis)

Adverse events of special interest

	Abiraterone acetate group (n=542)				Placebo group (n=540)*			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Fluid retention/oedema	161 (30%)	6 (1%)	0 (0%)	0 (0%)	123 (23%)	8 (1%)	1 (<1%)	0 (0%)
Hypokalaemia	87 (16%)	12 (2%)	2 (<1%)	0 (0%)	59 (11%)	10 (2%)	0 (0%)	0 (0%)
Hypertension	104 (19%)	25 (5%)	0 (0%)	0 (0%)	57 (11%)	17 (3%)	0 (0%)	0 (0%)
Cardiac disorders	81 (15%)	35 (6%)	6 (1%)	4 (<1%)	73 (14%)	17 (3%)	3 (<1%)	3 (<1%)
Atrial fibrillation	20 (4%)	8 (1%)	2 (<1%)	1 (<1%)	22 (4%)	5 (<1%)	0 (0%)	0 (0%)
ALT increased	40 (7%)	28 (5%)	4 (<1%)	0 (0%)	23 (4%)	3 (<1%)	1 (<1%)	0 (0%)
AST increased	47 (9%)	18 (3%)	0 (0%)	0 (0%)	21 (4%)	5 (<1%)	0 (0%)	0 (0%)

- Patients had low grade 3/4 fatigue (IA3: ABI, 2%; P, 2%) and no CNS impact

Overall safety data further support the favorable safety profile of ABI in chemotherapy-naïve mCRPC patients

ALT: alanine aminotransferase; AST: aspartate aminotransferase
*Before crossover

Ryan CJ, et al. *Lancet Oncol*. 2015;16:152–160;
Rathkopf et al. *Eur Urol* 2014;66(5):815-25

Comorbidità cardiovascolare: sicurezza di ABI confermata

- **Nessuna modifica nella LFEV**
- **Assenza di eventi cardiaci***
- **Nessuna sospensione del trattamento richiesta**
- **Abiraterone è risultato ben tollerato**

Follow up 21 mesi

Procopio
2013
Studio retrospettivo
51 pazienti

Cardiovascular safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients: a prospective evaluation

Veronica Prati[*,1,2], Ficerella Ruatta[1], Caterina Aversa[1], Angela Gennone[3], Danilo Galizia[4], Alessandro Bonzano[4], Sofia Torino[1], Imperia Nuzzolese[1], Laura Marandino[1], Massimo Aglietta[1] & Grazia Ortega[1,2]

Durante il trattamento con AA:

- **LVEF** mediana era 64% al basale e 63% dopo il trattamento (IC 95%: 0,05-2,08). Nessun paziente ha avuto una diminuzione della LVEF ≥10%.
- 4 (5%) dei pazienti ha sviluppato **ipertensione**, e in 26 pazienti con ipertensione preesistente (30%) è peggiorata;
- 2 pazienti (2%) hanno sviluppato **fibrillazione atriale**, che ha portato ad una temporanea interruzione del trattamento; **Non sono stati riportati casi di cardiopatia ischemica.**

Therapeutic Advances in Medical Oncology — Original Research

Safety of long-term exposure to abiraterone acetate in patients with castration-resistant prostate cancer and concomitant cardiovascular risk factors

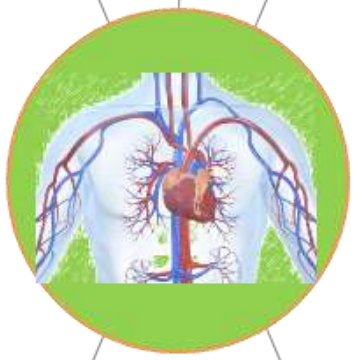
Elena Verzoni, Paolo Grassi, Raffaele Ratta, Monica Niger, Filippo De Braud, Riccardo Valdagni and Giuseppe Procopio

During the observation period, no CEs were recorded and no changes in LVEF were observed in the final echocardiographic evaluation

Verzoni
2016
Studio retrospettivo
51 pazienti

Follow up 4 anni

Prati-Ortega
2017
Studio prostettico
87 pazienti



Abiraterone acetate and prednisone in the pre- and post-docetaxel setting for metastatic castration-resistant prostate cancer: a mono-institutional experience focused on cardiovascular events and their impact on clinical outcomes

Alessia Cavo, Alessandra Rubagotti, Elisa Zanardi, Chiara Fabbroni, Linda Zinoli, Antonio Di Meglio, Eleonora Arboscello, Andrea Belodi, Paolo Spallarossa, Carlo Cattrini, Carlo Massimo and Francesco Boccardo

- Studio Retrospettivo che ha analizzato la safety di AA+P in pazienti con fibrillazione atriale post-docetaxel
  6 pazienti presentavano fibrillazione atriale (AF) all'inizio del trattamento
  - 4 AF permanente
  - 2 AF parossistica
- La durata mediana del trattamento con AA nei paziente con AF era 11,5 mesi (intervallo 4e22 mesi),

Rauch-Caffo
2016
Studio retrospettivo
7 pazienti con fibrillazione atriale

"no grade 1-4 adverse cardiac events were observed and no significant adjustment in the antihypertensive or diuretic medication was necessary"

Cavo-Boccardo
2017
Studio retrospettivo
105 pazienti

- **I pazienti che sviluppano AEs cardiovascolari traggono lo stesso beneficio da AA in termini di PFS e OS rispetto ai pazienti che non manifestano tali AEs**
- I pazienti che sviluppano Ipokaliemia sembrano vivere significativamente di più

Enzalutamide after chemotherapy in advanced castration-resistant prostate cancer: the Italian Named Patient Program

Francesca Maines*,[1], Ugo De Giorgi[2], Giuseppe Procopio[3], Gaetano Facchini[4], Lucia Fratino[5], Roberto Sabbatini[6], Donatello Gasparro[7], Umberto Basso[8], Claudia Mosillo[9], Enrico Campadelli[10], Francesco Massari[11], Teodoro Sava[12], Suzana Sirotova[13], Caterina Messina[14], Sarah Scagliarini[15], Vincenza Conteduca[2], Elena Verzoni[3], Sabrina Rossetti[4], Antonello Veccia[1], Stefania Kinspergher[1] & Orazio Caffo[1]

Real World

Table 2. Comorbidities of the patients enrolled in the Italian enzalutamide Named Patient Program.

Comorbidities	Number of patients (%)
Hypertension	82 (39.2)
Diabetes	16 (7.7)
Cardiac ischemia	11 (5.3)
Arrhythmia	15 (7.2)
Heart failure	2 (1.0)
Chronic obstructive pulmonary disease	11 (5.3)
Peripheral vascular disease	7 (3.3)
Cerebrovascular disease	2 (1.0)
Gastroduodenal ulcer	9 (4.3)
Chronic renal failure	9 (4.3)

Table 3. Recorded toxicities as assessed using National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0†.

Toxicities	All grades	1	2	3	4
Anemia	14 (6.7)	6 (2.9)	4 (1.9)	3 (1.4)	1 (0.5)
Thrombocytopenia	2 (1.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Nausea	5 (2.4)	3 (1.4)	1 (0.5)	1 (0.5)	0 (0.0)
Diarrhea	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Fatigue	42 (20.1)	26 (12.4)	11 (5.3)	5 (2.4)	0 (0.0)
Bone pain	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle pain	10 (4.8)	7 (3.3)	3 (1.4)	0 (0.0)	0 (0.0)
Edema	5 (2.4)	4 (1.9)	1 (0.5)	0 (0.0)	0 (0.0)
Hypertriglyceridemia	4 (1.9)	4 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	2 (1.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Transient ischemic attack	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)

†Percentages in brackets.

Maines F. et al. Future Oncol. 10.2217/fon-2018-0113C 2018

PROSTATE CANCER REGISTRY

Around 80% of patients received multiple drugs

Prospective, non-interventional, multicentre registry of > 3,000 men with mCRPC (199 centres/16 countries in Europe)

Patient characteristics at study entry

Characteristics	Chemotherapy naive (n = 876)	Post chemotherapy (n = 498)	Total (N = 1,374)
Age, years, mean (SD)	**73.1 (8.27)**	**71.6 (7.57)**	**72.6 (8.06)**
ECOG PS, n (%)	n = 828	n = 458	n = 1,286
0	343 (41.4)	149 (32.5)	492 (38.3)
1	373 (45.0)	236 (51.5)	609 (47.4)
≥ 2	112 (13.5)	73 (15.9)	185 (14.4)
Concomitant therapies , n (%)	n = 876	n = 498	n = 1374
Any	**680 (77.6)**	**404 (81.1)**	**1,084 (78.9)**
Cardiovascular disease therapies	514 (58.7)	284 (57.0)	798 (58.1)
Antihypertensives	428 (48.9)	225 (45.2)	653 (47.5)
Analgesics	361 (41.2)	243 (48.8)	604 (44.0)
Diabetes therapies	124 (14.2)	86 (17.3)	210 (15.3)
Antithrombotic agents	86 (9.8)	62 (12.4)	148 (10.8)
Nervous system disorder therapies	42 (4.8)	15 (3.0)	57 (4.1)
Anti-infective agents	14 (1.6)	21 (4.2)	35 (2.5)
Growth factors	9 (1.0)	15 (3.0)	24 (1.7)
Blood substitutes	4 (0.5)	10 (2.0)	14 (1.0)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Chowdhury S, et al. Poster presented at ESMO 2016. Poster 746P. NCT02236637

4.5 Interazioni con altri medicinali (da RCP)

Abiraterone	Enzalutamide
Analgesici (es. codeina, ossicodone, tramadolo)	**Analgesici** (es. fentanyl, tramadolo)
Antibiotici (es. rifampicina, rifapentina, rifabutina, telitromicina)	**Antibiotici** (es. claritromicina, doxiciclina)
Antineoplastici NON RIPORTATO*	**Antineoplastici** (es. cabazitaxel)
Anticoagulanti NON RIPORTATO*	**Anticoagulanti** (es. acenocumarolo, warfarin)
Antiepilettici (es. fenitoina, carbamazepina, fenobarbitale)	**Antiepilettici** (es. carbamazepina, clonazepam, fenitoina, primidone, valproato)
Antipsicotici (es. Erba di San Giovanni, aloperidolo, risperidone, tioridazina)	**Antipsicotici** (es. aloperidolo)
Betabloccanti (es. metoprololo, propranololo)	**Betabloccanti** (es. bisprololo, propranololo)
Calcioantagonisti NON RIPORTATO*	**Calcioantagonisti** (es. diltiazem, felodipina, nicardipina, nifedipina, verapamil)
Glicosidi cardiaci NON RIPORTATO*	**Glicosidi cardiaci** (es. digossina)
Corticosteroidi NON RIPORTATO*	**Corticosteroidi** (es. desametasone, prednisolone)
Antivirali HIV NON RIPORTATO*	**Antivirali HIV** (es. indinavir, ritonavir)
Ipnotici e antidepressivi (es. desipramina, venlafaxina)	**Ipnotici e antidepressivi** (es. diazepam, midazolam, zolpidem)
Statine NON RIPORTATO*	**Statine metabolizzate da CYP3A4** (es. atrovastatina, simvastatina)
Farmaci tiroidei NON RIPORTATO*	**Farmaci tiroidei** (es. levotiroxina)
Antiaritmici (es. propafenone, flecanide)	**Antiaritmici NON RIPORTATO***

*ad oggi non ci sono dati clinici o segnalazioni che documentino tale interazione, quindi non è possibile affermare con certezza che abiraterone non interagisca con questa classe di farmaci

Riassunto delle caratteristiche del prodotto di Xtandi
Riassunto delle caratteristiche del prodotto di Zytiga

Terapie ormonali di nuova generazione
ABIRATERONE - ENZALUTAMIDE

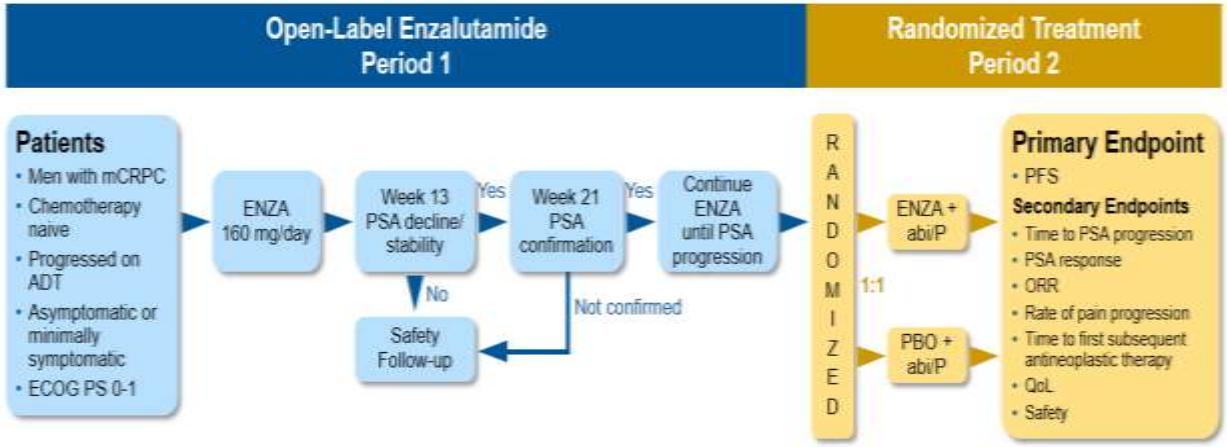
- Efficacia
- Tossicità
- **Sequenze**
- Fattori predittivi
- Prospettive future

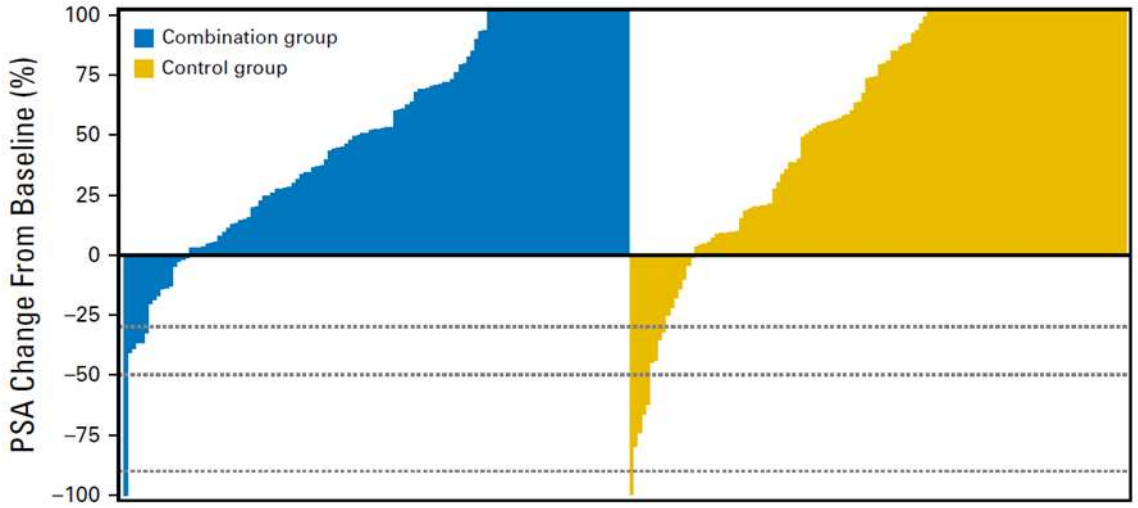
	Cohort size	Prior treatment	PSA response	RX response	Survival	Comments
ABIRATERONE POST-ENZALUTAMIDE						
Loriot *et al.*[1]	38	Not reported	**30% PSA decline:** 7/38 (18%) **50% PSA decline:** 3/38 (8%)	**Partial response:** 1/12 (8%)	**Overall survival:** 7.2 m (95% CI: 5–NR) **PFS:** 2.7 m (95% CI: 2.3–4.1)	No difference in response to abiraterone in responders vs. non-responders to previous enzalutamide
Noonan *et al.*[2]	30	Anti-androgens: 97.4% Docetaxel: 100% Mitoxantrone: 2.6%	**30% PSA decline:** 3/27 (11%) **50% PSA decline:** 1/27 (3%)	**Partial response:** 0%	**Overall survival:** 11.6m (95% CI: 6.5–16.6) **PFS:** 3.6 m (95% CI: 2.5–4.7)	1 patient (5%) with previous 30% PSA decline on enzalutamide achieved a 30% PSA decline on abiraterone
ENZALUTAMIDE POST-ABIRATERONE						
Schrader *et al.*[3]	35	Abiraterone: 100% Docetaxel: 100% Cabazitaxel: 2.8%	**30% PSA decline:** NR **50% PSA decline:** 10/35 (28.6%)	**Partial response:** 1/17 (5.9%)	**Overall survival:** 7.1 m (95% CI: 6.2–8.1)* **PFS:** Not reported	Response to previous abiraterone not predictive of response to enzalutamide
Bianchini *et al.*[4]	39	Anti-androgens: 89.7% Abiraterone: 100% Docetaxel: 100% Cabazitaxel: 35.8%	**30% PSA decline:** 16/39 (41%) **50% PSA decline:** 5/39 (12.8%)	**Partial response:** 1/23 (4.3%)	**Overall survival:** Median OS not reached **PFS:** 2.8 m (95% CI: 2–3.6)	No association between 50% PSA response on abiraterone and 50% PSA response on enzalutamide
Thomsen *et al.*[5]	24	Abiraterone: 100% Docetaxel: 100% Cabazitaxel: 33.3%	**30% PSA decline:** 11/24 (46%) **50% PSA decline:** 4/24 (16.7%)	Not reported	**Overall survival:** 4.8 m (95% CI: 3–8.4) **PFS:** Not reported	Non-significant trend associating response to abiraterone with response to enzalutamide (p=0.05). Significantly worse PSA response in post-cabazitaxel patients (p=0.03)
Badrising *et al.*[6]	61	Abiraterone: 100% Docetaxel: 100% Mitoxantrone: 3% Cabazitaxel: 30%	**30% PSA decline:** 28/61 (46%) **50% PSA decline:** 13/61 (21%)	Not reported	**Overall survival:** 7.3 m (95% CI: 6.6–NR) **PFS:** 2.8 m (95% CI: 2.6–3.7) **PSA PFS:** 4 m (95% CI: 3.7–NR)	No significant difference in PSA response or time on treatment between previous responders and non-responders to abiraterone
Azad *et al.*[7]	115	Abiraterone: 100% Docetaxel: 59%	**50% PSA decline:** 27/115 (23.5%)	Not reported	**Overall survival:***** 10.6 m **PFS:** 5.3 m	No difference in PSA or OS in patients treated with previous docetaxel vs. docetaxel-naïve

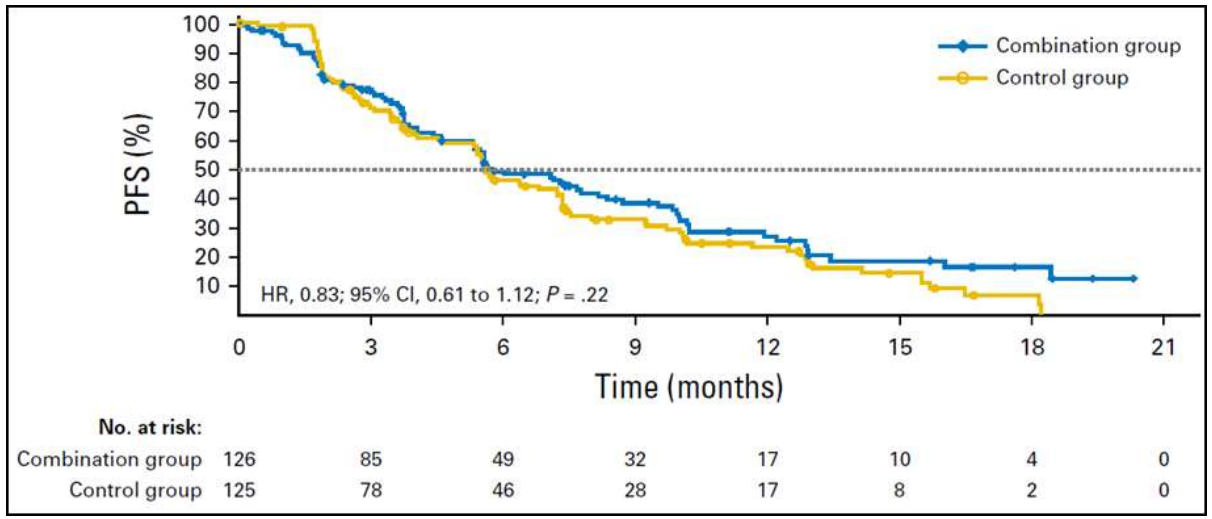
CI=confidence interval; m=months; NR=not recorded; OS=overall survival; PFS=progression-free survival; PSA=prostate-specific antigen; Rx=radiographic.

1. Loriot Y, *et al. Ann Oncol* 2013;24:1807–12; 2. Noonan KL, *et al. Ann Oncol* 2013;24:1802–7; 3. Schrader AJ, *et al. Eur Urol* 2014;65:30–6; 4. Bianchini D, *et al. Eur J Cancer* 2014;50:78–84; 5. Thomsen FB, *et al. Scand J Urol* 2014;48:268–75; 6. Badrising S, *et al. Cancer* 2014;120:968–75; 7. Azad A, *et al. Eur Urol* 2015;67:23–9.

PLATO prospective trial







Combination Group: ENZA + ABI/p

Control Group: ABI/p + PBO

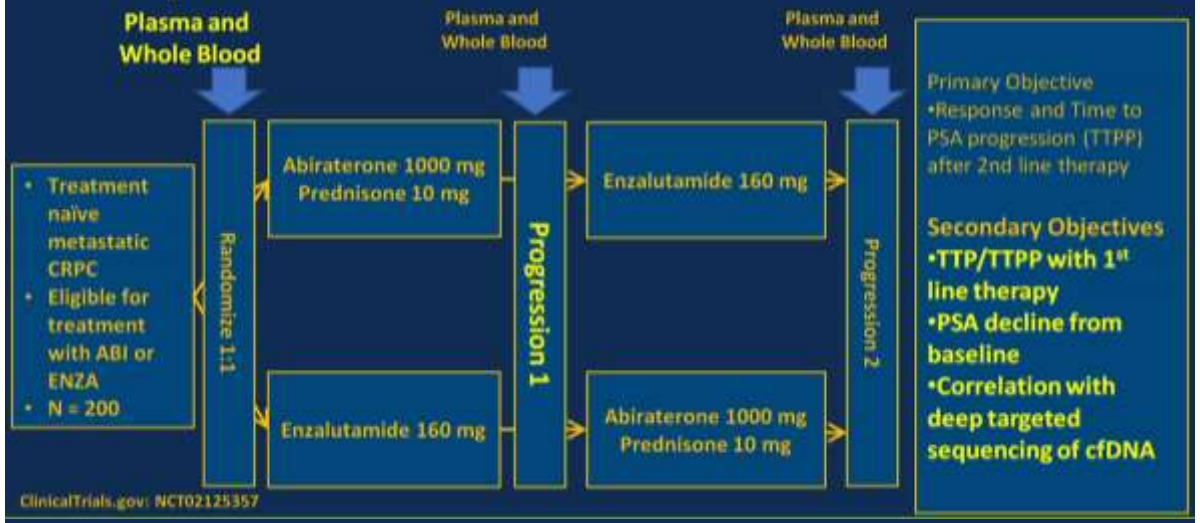
Attard G et al. *J Clin Oncol.* 2017;35 (suppl; abstr 5004).

Attard G et al. J Clin Oncol. 2018 Sep 1;36(25):2639-2646

A randomized phase II cross-over study of abiraterone + prednisone vs enzalutamide for patients with metastatic, castration-resistant prostate cancer

Kim N. Chi, Matti Annala, Katherine Sunderland, Daniel Khalaf, Daygen Finch, Conrad D. Oja, Joanna Vergidis, Muhammad Zulfiqar, Kevin Beja, Gillian Vandekerkhove, Martin Gleave, Alexander W. Wyatt

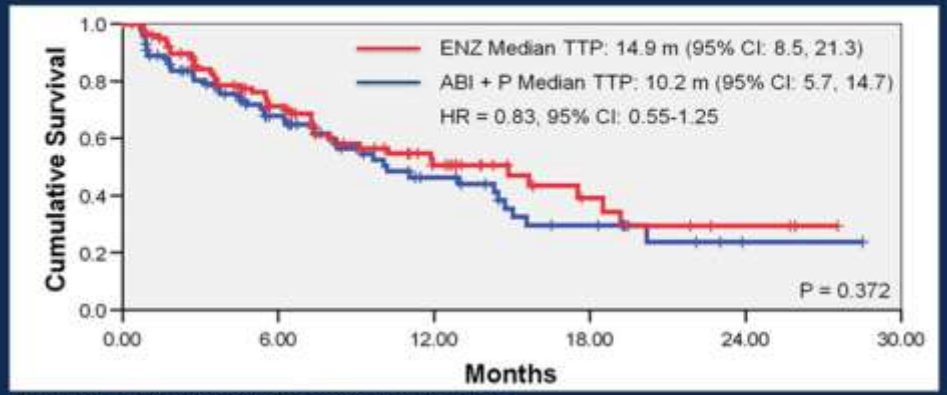
Study Schema



Best PSA decline: 12 weeks

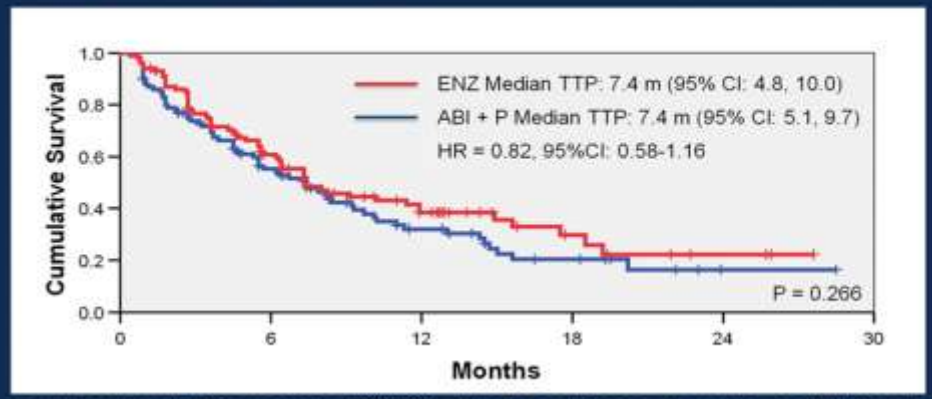
	Abiraterone + P N=99	Enzalutamide N=98	P-value
PSA Decline ≥ 30%	64 (65%)	83 (85%)	0.0012
PSA Decline ≥ 50%	54 (55%)	75 (77%)	0.0012
No PSA Decline	20 (20%)	10 (10%)	0.0501

Time to PSA Progression (Confirmed)

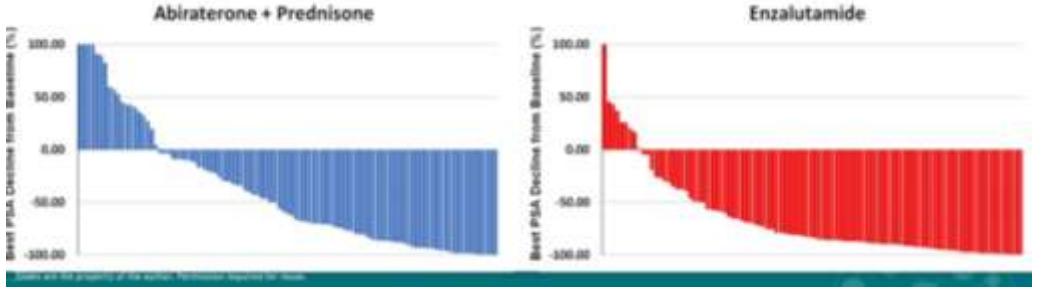


*PCWG3: ≥ 25% and ≥ 2 ng/mL above nadir/baseline

Time to Progression



*First of confirmed PSA progression (PCWG3), clinical or radiological progression, or death from disease



Presented By Kim Chi at 2017 ASCO Annual Meeting

Systemic Options for mCRPC after Progression on Intensified Treatment of mHSPC

2015 (CHAARTED, STAMPEDE)	➔ ~~Doce~~/Abi/Enza/Caba ➔ Caba/Enza/Abi ➔ Caba/Abi/Enza/Ra-223
2017 (LATITUDE, STAMPEDE)	➔ ~~Abi/Enza~~/Doce ➔ Caba/Enza ➔ Caba/Enza/Ra-223
2018 (ENZAMET, TITAN, ARASENS	➔ ~~Enza/Abi~~/Doce ➔ Caba/Abi ➔ Caba/Abi/Ra-223

ENZAMET (enzalutamide), TITAN (apalutamide), ARASENS (darolutamide)
Ra-223:Symptomatic mCRPC when applicable

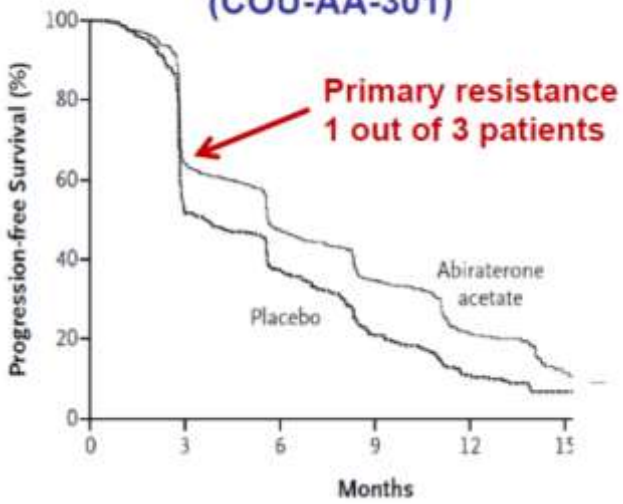
Facchini G.

Terapie ormonali di nuova generazione
ABIRATERONE - ENZALUTAMIDE

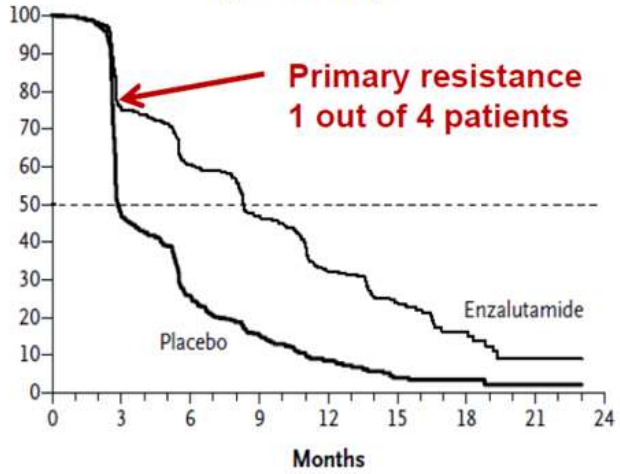
- Efficacia
- Tossicità
- Sequenze
- **Fattori predittivi**
- Prospettive future

Not all the patients respond to new hormonal agents

Abiraterone[1] (COU-AA-301)

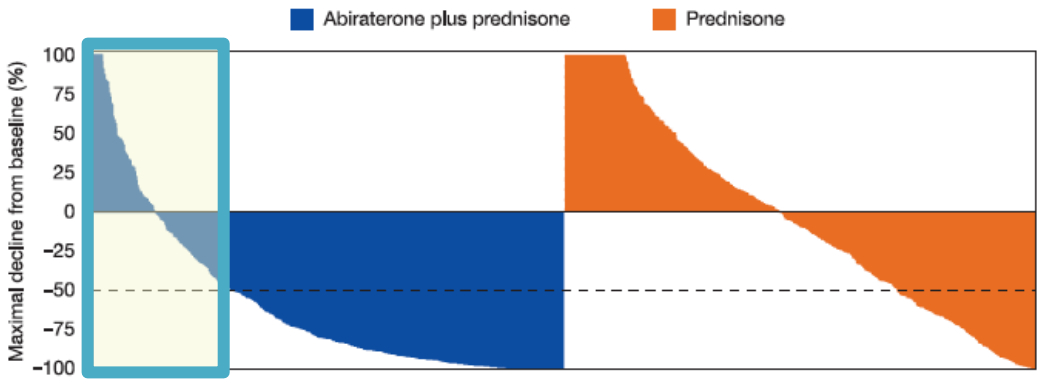


Enzalutamide[2] (AFFIRM)

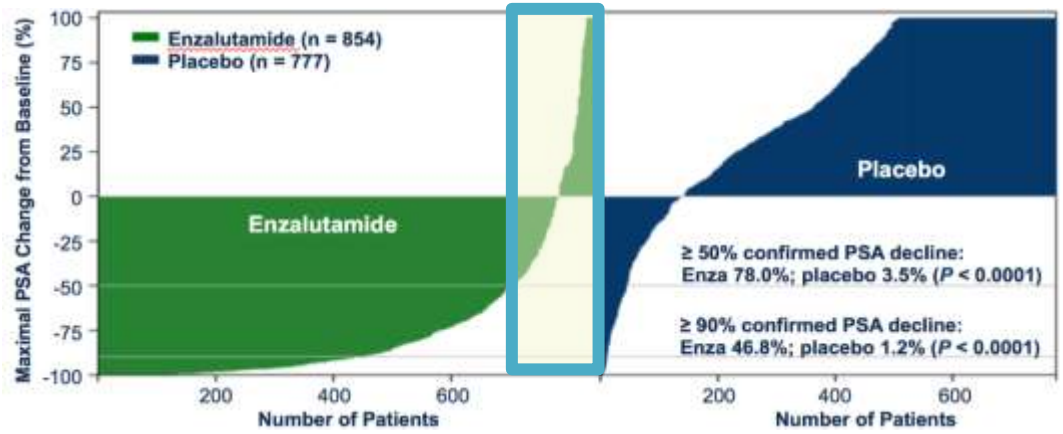


De Bono et al. N Engl J Med 2011; 364: 1995–2005
Scher H et al. N Engl J Med 2012 (epub ahead of print)

Abiraterone (COU-AA-302)[1]

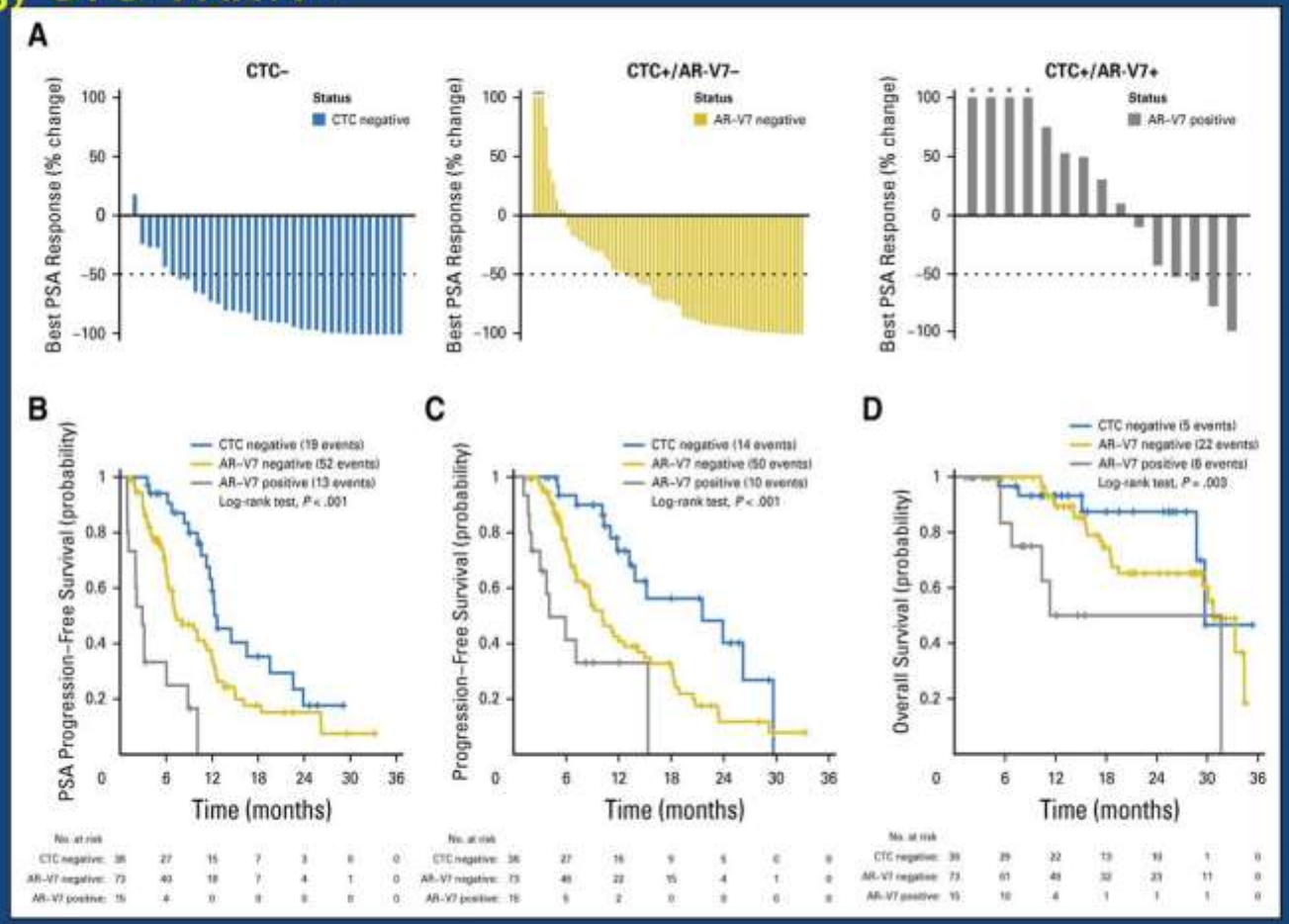


Enzalutamide (PREVAIL)[2]



1. Rathkopf DE et al. Eur Urol 2014
2. Armstrong A et al. J Clin Oncol 2014 :abstract 5007 (podium)

First line treatment Abiraterone or Enzalutamide for CTC-neg, CTC+/ARV7-neg, CTC+/ARV7+



Frist Line (n=124)

CTC-neg 86.1%
CTC+/ARV7-neg 65.8%
CTC+/ARV7+ 26.7%

Antonarakis ES et al;
JCO **2017**, 35, 2149-2156

Presented By Mary-Ellen Taplin at 2018 ASCO Annual Meeting

Terapie ormonali di nuova generazione
ABIRATERONE - ENZALUTAMIDE

- Efficacia
- Tossicità
- Sequenze
- Selezione del paziente
- Fattori predittivi
- **Prospettive future**

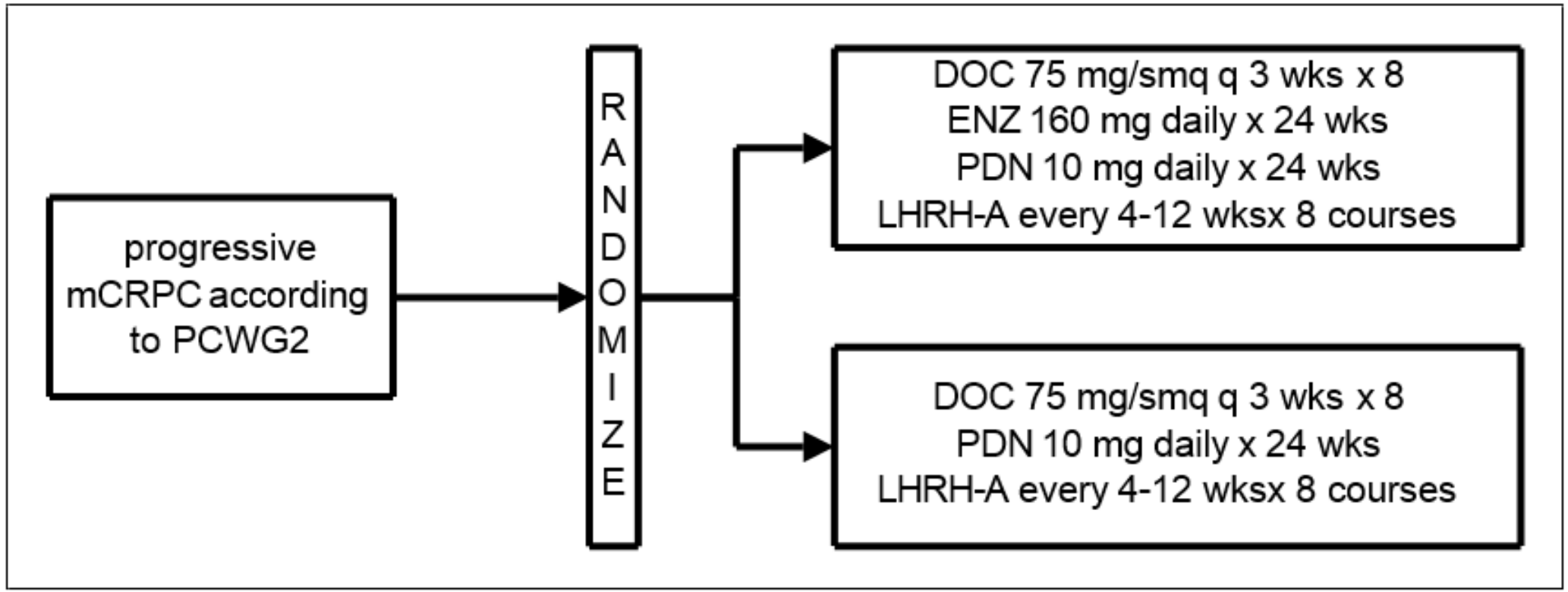
56021927PCR3001-Study Design

Randomized, DB, Placebo Control

[a]Stratification factors:

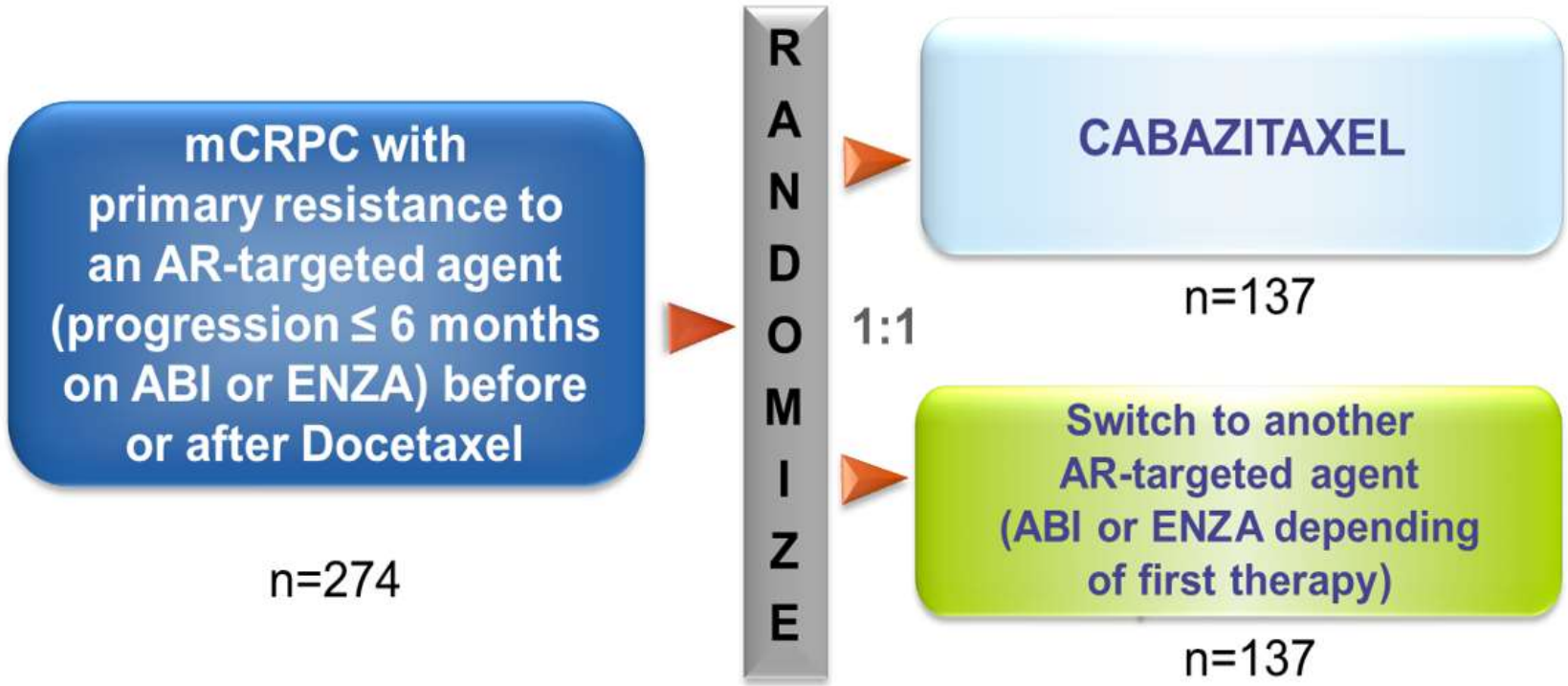
- Baseline ECOG 0 vs. 1
- Region (NA, EU, ROW)
- Presence/absence of visceral disease

CHemotherapy plus Enzalutamide In first line therapy for castration Resistant prOstate caNcer



A multicentric Randomized phase II study.

CARD – Study design



Stratification Factors: Eastern Cooperative Oncology Group (ECOG) performance status (**0-1 Vs. 2**), extent of metastatic spread (**low Vs. high**) and timing of AR targeted agent (**before Vs. after docetaxel**).

- High volume metastatic disease is defined as: Visceral metastases and/or ≥ 4 bone metastases (with at least one beyond pelvis and vertebral column).
- Low volume metastatic disease is defined as: No visceral metastases and < 4 bone metastases.

CHAARTED-2 Trial: Abiraterone +/- Cabazitaxel for Extensive Disease Following Docetaxel

Patients
Screening Phase 28 Days

Eligibility:
- Previous ADT/Docetaxel for Hormone-naïve mPCa

Stratified by:
- ECOG PS 0 vs. 1-2
- Time to CRPC <12 to >12 mos
- Bone only vs. visceral

RANDOMIZED

Arm A:
Abiraterone 1000mg/day + Cabazitaxel 25mg/m^2 every 3 weeks

Arm B:
Abiraterone 1000mg/day

Evaluate every 3 weeks for first 18 weeks, and every 12 weeks thereafter

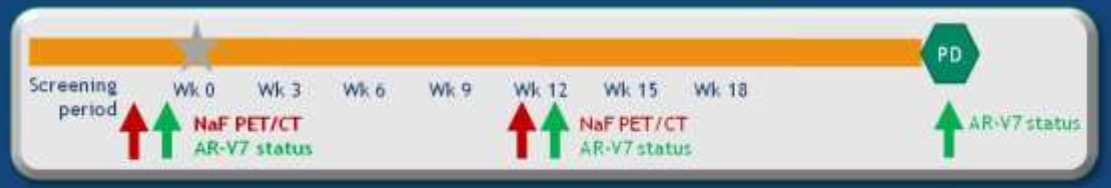
Efficacy end points

Primary:
- PFS

Secondary:
- OS
- PSA response
- Time to PSA progression
- Radiographic response
- Safety

210 PATIENTS RANDOMIZED (1:1)

All patients will continue ADT as per SOC
All patients will receive Prednisone 5mg twice daily



www.clinicaltrials.gov: CHAARTED-2 (NCT03419234)

PI: Christos E. Kyriakopoulos, MD

Presented By Neeraj Agarwal at 2018 ASCO Annual Meeting

QUESITO CLINICO N°19:

Nei pazienti affetti da CRPC metastatico "chemo-naïve" asintomatici o paucisintomatici, non suscettibili di indicazioni al trattamento chemioterapico, Enzalutamide e Abiraterone Acetato sono sempre opzioni preferibili alla sola osservazione in termini di sopravvivenza globale?

Qualità dell'evidenza SIGN	Raccomandazione	Forza della raccomandazione clinica
Alta	Nei pazienti metastatici resistenti alla castrazione, asintomatici o paucisintomatici, dovrebbe sempre essere preso in considerazione il trattamento con Abiraterone acetato (e prednisone) o con Enzalutamide, specie se si ritenga preferibile differire l'uso della chemioterapia con Docetaxel [90-93].	Positiva forte

La qualità dell'evidenza è alta in quanto deriva da studi prospettici randomizzati, condotti su di un numero adeguato di pazienti.

Qualità dell'evidenza SIGN	Raccomandazione	Forza della raccomandazione clinica
Moderata	Nei pazienti con malattia metastatica, resistente alla castrazione, in progressione dopo Docetaxel, che non si ritenga di candidare a chemioterapia di seconda linea con Cabazitaxel, può essere preso in considerazione il trattamento sia con Abiraterone acetato che con Enzalutamide. La scelta è in funzione dell'eventuale trattamento pre-docetaxel con uno dei due farmaci e/o di specifiche controindicazioni all'uso del prednisone (nel caso dell'abiraterone acetato) o di enzalutamide (precedenti eventi ischemici cerebrali o anamnesi positiva per crisi comiziali) [98, 99].	**Positiva debole**

La qualità dell'evidenza è moderata causa indirectness del confronto.

Qualità dell'evidenza SIGN	Raccomandazione	Forza della raccomandazione clinica
Molto Bassa	Nei pazienti affetti da malattia metastatica resistente alla castrazione, allo stato attuale delle conoscenze, non dovrebbe essere preferita una sequenza terapeutica rispetto ad altre. La scelta dei trattamenti da utilizzare dovrebbe essere effettuata sulla base delle caratteristiche della malattia, della sintomaticità/asintomaticità del paziente, delle sue preferenze, dell'idoneità a ricevere un trattamento chemioterapico [94, 98, 99, 102-112]	**Negativa debole**

La qualità dell'evidenza è molto bassa, in quanto non sono attualmente disponibili studi randomizzati o solidi studi prospettici di coorte che abbiano confrontato gli outcome dei pazienti sottoposti a differenti sequenze di agenti terapeutici. L'evidenza deriva pertanto esclusivamente da dati retrospettivi su casistiche piccole e selezionate.


Grazie