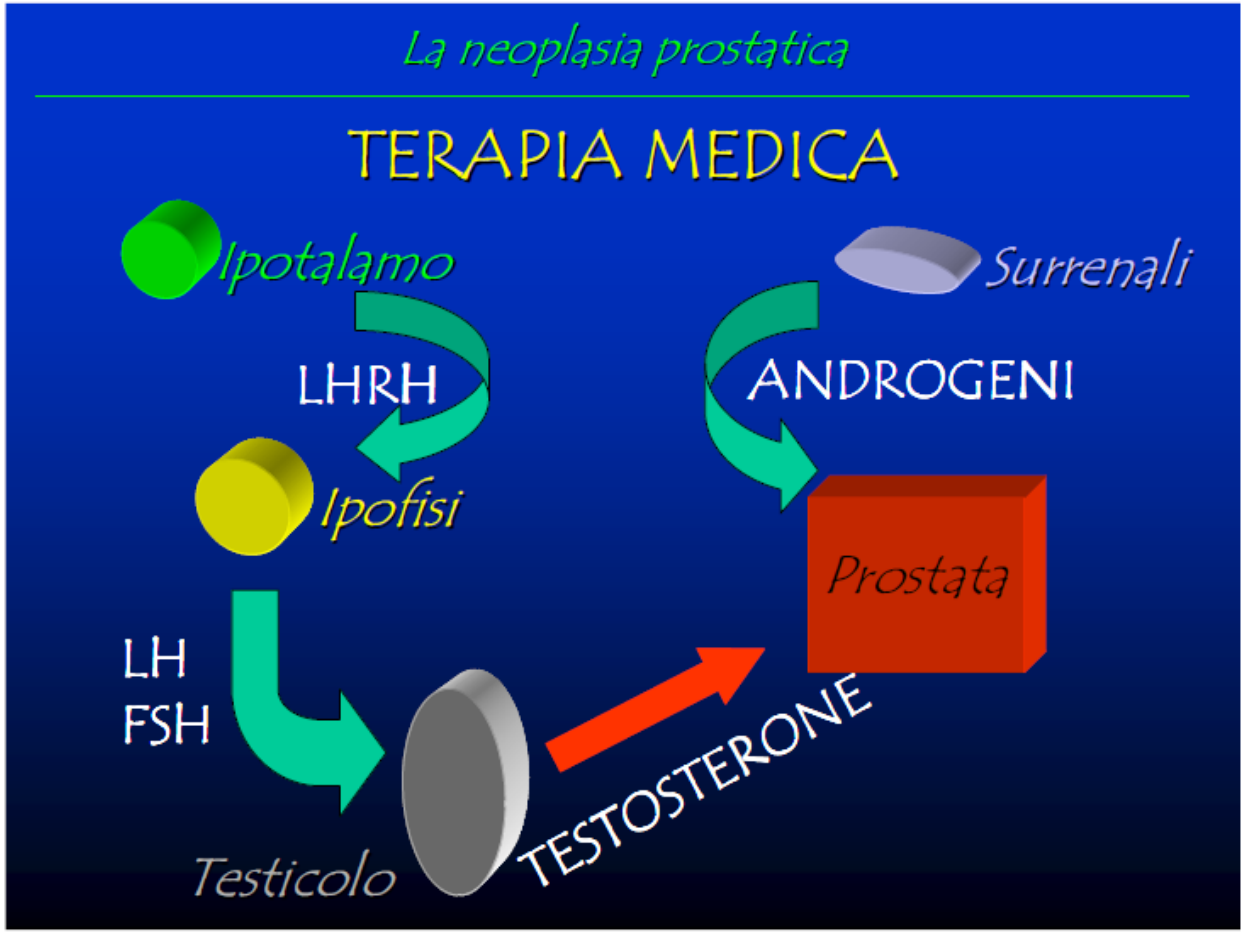
Carcinoma della prostata: quali novità per il 2015?

Carcinoma prostatico avanzato: linee guida AIOM

M. Nicodemo Oncologia “S. Cuore-Don Calabria”

Negrar 1 Aprile 2015


La neoplasia prostatica
TERAPIA MEDICA
Ipotalamo
Surrenali
LHRH
ANDROGENI
Ipofisi
Prostata
LH
FSH
Testicolo
TESTOSTERONE

5.4.1 Terapia della malattia ormonosensibile ("hormone-sensitive/dependent")

5.4.1.1 Deprivazione androgenica

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
D	Nei pazienti M1 candidati a terapia androgeno-deprivativa, se sintomatici o comunque a rischio di flare-up, il trattamento con LH-RH agonisti deve essere preceduto da antiandrogeno puro, proseguito poi solo per le prime 4 settimane di trattamento	**Positiva forte**
B	In alternativa al trattamento con LH-RH agonisti, negli stessi pazienti (M1, a richio di flare-up), può essere utilizzata la terapia con LH-RH antagonista	**Positiva debole**

5.4.1 Terapia della malattia ormonosensibile ("hormone-sensitive/dependent")

5.4.1.2 Monoterapia con antiandrogeni

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
B	La monoterapia con Bicalutamide non dovrebbe essere utilizzata nei pazienti M1*.	**Negativa debole**

** Il trattamento con Bicalutamide in monoterapia può essere utilizzato nei pazienti M0 che desiderino, o in cui sia opportuno, evitare il più a lungo possibile gli effetti della castrazione (forza della raccomandazione: positiva debole)*

5.4.1 Terapia della malattia ormonosensibile ("hormone-sensitive/dependent")

5.4.1.3 Blocco androgenico totale

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
B	Nei pazienti metastatici (M1), candidati inizialmente a terapia endocrina, il trattamento continuativo con un antiandrogeno non steroideo in aggiunta alla castrazione (BAT: Blocco Androgenico Totale) può essere preferibile alla sola castrazione, in assenza di controindicazioni all'uso degli antiandrogeni e se ben tollerato.	**Positiva Debole**

Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

- Considering the possible minimal survival benefit together with the cost and toxicity of the additional anti-androgen, first-line hormonal management of metastatic prostate cancer should be based on chemical or surgical castration only [I, B].
- Patients who develop castration-resistant prostate cancer (CRPC) should continue androgen suppression and be considered for further hormone therapies; chemotherapy might be preferable in those with poor initial hormone response or severe symptoms. In patients progressing following docetaxel, treatment with abiraterone, or enzalutamide, should be discussed if not used previously [II, A].
- Docetaxel using a 3-weekly schedule should be considered for symptomatic, castration-resistant disease [I, A].
- Cabazitaxel is more effective than mitoxantrone in patients previously treated with docetaxel [I, B].
- External beam RT should be offered for patients with a moderate number of painful bone metastases (1×8 Gy has equal pain-reducing efficacy to multifraction schedules) [I, A].
- Bone targeted therapy with one of the beta particle emitting radionuclides should be considered for patients with painful bone metastases [II, B].
- In patients with bone metastases from CRPC at high risk for clinically relevant SREs, denosumab or zoledronic acid can be recommended, and a large trial found that denosumab delayed SREs for longer than zoledronic acid. Neither agent has been shown to prolong survival [I, B].
- MRI of the spine to detect subclinical cord compression should be considered in men with CRPC with vertebral metastases and back pain [III, B].

5.4.1 Terapia della malattia ormonosensibile ("hormone-sensitive/dependent")

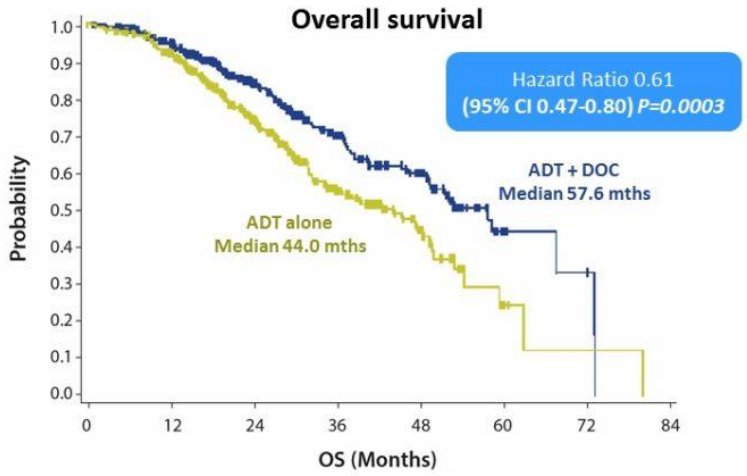
5.4.1.4 Trattamento intermittente o continuativo?

Qualità dell'evidenza SIGN	Raccomandazione	Forza della raccomandazione clinica
A	La deprivazione androgenica intermittente non deve essere utilizzata in sostituzione dell'approccio continuativo nei pazienti M1.	**Negativa forte**
B	La deprivazione androgenica intermittente può rappresentare una alternativa terapeutica nei pazienti M0, dopo adeguata verifica della responsività al trattamento ormonale di prima linea.	**Positiva debole**

5.4.1 Terapia della malattia ormonosensibile ("hormone-sensitive/dependent")

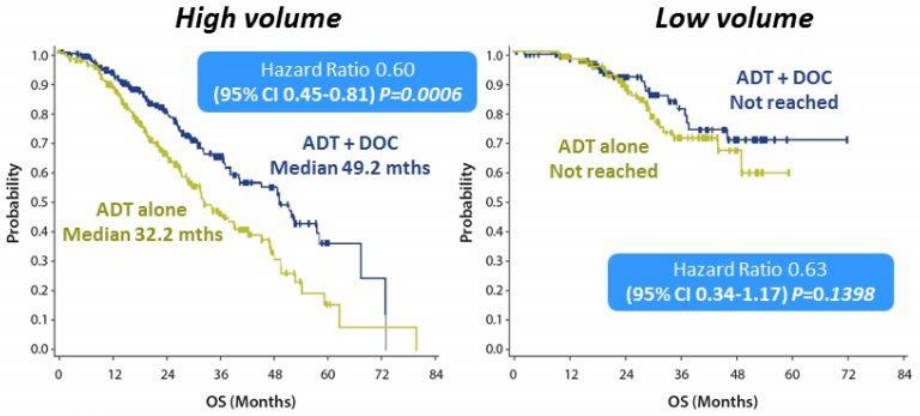
5.4.1.5 Chemioterapia

Primary endpoint: overall survival



Sweeney C et al. J Clin Oncol 2014;32(June 20 suppl):abstract LBA2
ADT: androgen deprivation therapy; DOC: docétaxel; OS: overall survival; mths: months

Overall survival by extent of metastatic disease at start of ADT



17-month benefit in median OS (from 32.2 to 49.2 months) for high volume disease

Sweeney C et al. J Clin Oncol 2014;32(June 20 suppl):abstract LBA2
ADT: androgen deprivation therapy; DOC: docétaxel 75mg/m²

5.4.2 Terapia della malattia resistente alla castrazione (CRPC)

Table 20.1: Definition of CRPC

Castrate serum testosterone < 50 ng/ml or 1.7 nmol/L plus either: Biochemical progression: Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA > 2 ng/mL. or Radiological progression: The appearance of two or more bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in solid tumours) (22).

Guidelines on

Prostate Cancer

N. Mottet (chair), P.J. Bastian, J. Bellmunt,
R.C.N. van den Bergh, M. Bolla, N.J. van Casteren, P. Cornford,
S. Joniau, M.D. Mason, V. Matveev, T.H. van der Kwast,
H. van der Poel, O. Rouvière, T. Wiegel

5.4.2 Terapia della malattia resistente alla castrazione (CRPC)

5.4.2.3 Terapia ormonale di seconda linea con farmaci di I generazione

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
D	Nei pazienti in progressione durante BAT è raccomandabile un periodo adeguato (4-6 settimane) di sospensione del trattamento con l'antiandrogeno puro che si sta utilizzando	**Positiva debole**
D	In pazienti in progressione dopo withdrawal dell'antiandrogeno, sono possibili ulteriori manipolazioni ormonali con farmaci di I generazione purchè non sia presente un'evoluzione troppo rapida di malattia	**Positiva debole**

5.4.2 Terapia della malattia resistente alla castrazione (CRPC)

5.4.2.5 Chemioterapia di I linea

Qualità dell'evidenza SIGN	Raccomandazione	Forza della raccomandazione clinica
A	I pazienti metastatici resistenti alla castrazione, in progressione di malattia, devono essere valutati per un trattamento con docetaxel e prednisone, quando possibile secondo schedula trisettimanale.	**Positiva forte**

5.4.2 Terapia della malattia resistente alla castrazione (CRPC)

5.4.2.4 Terapia ormonale di seconda linea con farmaci di nuova generazione

Qualità dell'evidenza SIGN	Raccomandazione	Forza della raccomandazione clinica
B	I pazienti metastatici resistenti alla castrazione e affetti da malattia asintomatica o paucisintomatica, a progressione di malattia dovrebbero essere valutati per il trattamento con abiraterone acetato (e prednisone), farmaco in grado di influenzare favorevolmente la loro speranza di vita e di ritardare nel tempo la necessità di ricorrere alla chemioterapia.	Positiva debole

ORIGINAL ARTICLE

Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy

Charles J. Ryan, M.D., Matthew R. Smith, M.D., Ph.D., Johann S. de Bono, M.B., Ch.B., Ph.D., Arturo Molina, M.D., Christopher J. Logothetis, M.D., Paul de Souza, M.B., Ph.D., Karim Fizazi, M.D., Ph.D., Paul Mainwaring, M.D., Josep M. Piulats, M.D., Ph.D., Siobhan Ng, M.D., Joan Carles, M.D., Peter F.A. Mulders, M.D., Ph.D., Ethan Basch, M.D., Eric J. Small, M.D., Fred Saad, M.D., Dirk Schrijvers, M.D., Ph.D., Hendrik Van Poppel, M.D., Ph.D., Som D. Mukherjee, M.D., Henrik Suttmann, M.D., Winald R. Gerritsen, M.D., Ph.D., Thomas W. Flaig, M.D., Daniel J. George, M.D., Evan Y. Yu, M.D., Eleni Efstathiou, M.D., Ph.D., Allan Pantuck, M.D., Eric Winquist, M.D., Celestia S. Higano, M.D., Mary-Ellen Taplin, M.D., Youn Park, Ph.D., Thian Kheoh, Ph.D., Thomas Griffin, M.D., Howard I. Scher, M.D., and Dana E. Rathkopf, M.D., for the COU-AA-302 Investigators*

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Ryan at the Genitourinary Medical Oncology Program, UCSF Helen Diller Family Comprehensive Cancer Center, 1600 Divisadero St., San Francisco, CA 94115, or at ryanc@medicine.ucsf.edu.

*Additional investigators in the COU-AA-302 study are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on December 10, 2012, and updated on January 17, 2013, at NEJM.org.

N Engl J Med 2013;368:138-48.
DOI: 10.1056/NEJMoa1209096

ABSTRACT

BACKGROUND

Abiraterone acetate, an androgen biosynthesis inhibitor, improves overall survival in patients with metastatic castration-resistant prostate cancer after chemotherapy. We evaluated this agent in patients who had not received previous chemotherapy.

METHODS

In this double-blind study, we randomly assigned 1088 patients to receive abiraterone acetate (1000 mg) plus prednisone (5 mg twice daily) or placebo plus prednisone. The coprimary end points were radiographic progression-free survival and overall survival.

RESULTS

The study was unblinded after a planned interim analysis that was performed after 43% of the expected deaths had occurred. The median radiographic progression-free survival was 16.5 months with abiraterone–prednisone and 8.3 months with prednisone alone (hazard ratio for abiraterone–prednisone vs. prednisone alone, 0.53; 95% confidence interval [CI], 0.45 to 0.62; P<0.001). Over a median follow-up period of 22.2 months, overall survival was improved with abiraterone–prednisone (median not reached, vs. 27.2 months for prednisone alone; hazard ratio, 0.75; 95% CI, 0.61 to 0.93; P=0.01) but did not cross the efficacy boundary. Abiraterone–prednisone showed superiority over prednisone alone with respect to time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, prostate-specific antigen progression, and decline in performance status. Grade 3 or 4 mineralocorticoid-related adverse events and abnormalities on liver-function testing were more common with abiraterone–prednisone.

CONCLUSIONS

Abiraterone improved radiographic progression-free survival, showed a trend toward improved overall survival, and significantly delayed clinical decline and initiation of chemotherapy in patients with metastatic castration-resistant prostate cancer. (Funded by Janssen Research and Development, formerly Cougar Biotechnology; ClinicalTrials.gov number, NCT00887198.)

ORIGINAL ARTICLE

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*

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Beer at OHSU Knight Cancer Institute, Oregon Health and Science University, 3303 SW Bond Ave., CH14R, Portland, OR 97239, or at beert@ohsu.edu.

*Additional investigators in the PREVAIL study are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on June 1, 2014, at NEJM.org.

N Engl J Med 2014;371:424-33.
DOI: 10.1056/NEJMoa1405095

ABSTRACT

BACKGROUND

Enzalutamide is an oral androgen-receptor inhibitor that prolongs survival in men with metastatic castration-resistant prostate cancer in whom the disease has progressed after chemotherapy. New treatment options are needed for patients with metastatic prostate cancer who have not received chemotherapy, in whom the disease has progressed despite androgen-deprivation therapy.

METHODS

In this double-blind, phase 3 study, we randomly assigned 1717 patients to receive either enzalutamide (at a dose of 160 mg) or placebo once daily. The coprimary end points were radiographic progression-free survival and overall survival.

RESULTS

The study was stopped after a planned interim analysis, conducted when 540 deaths had been reported, showed a benefit of the active treatment. The rate of radiographic progression-free survival at 12 months was 65% among patients treated with enzalutamide, as compared with 14% among patients receiving placebo (81% risk reduction; hazard ratio in the enzalutamide group, 0.19; 95% confidence interval [CI], 0.15 to 0.23; P<0.001). A total of 626 patients (72%) in the enzalutamide group, as compared with 532 patients (63%) in the placebo group, were alive at the data-cutoff date (29% reduction in the risk of death; hazard ratio, 0.71; 95% CI, 0.60 to 0.84; P<0.001). The benefit of enzalutamide was shown with respect to all secondary end points, including the time until the initiation of cytotoxic chemotherapy (hazard ratio, 0.35), the time until the first skeletal-related event (hazard ratio, 0.72), a complete or partial soft-tissue response (59% vs. 5%), the time until prostate-specific antigen (PSA) progression (hazard ratio, 0.17), and a rate of decline of at least 50% in PSA (78% vs. 3%) (P<0.001 for all comparisons). Fatigue and hypertension were the most common clinically relevant adverse events associated with enzalutamide treatment.

CONCLUSIONS

Enzalutamide significantly decreased the risk of radiographic progression and death and delayed the initiation of chemotherapy in men with metastatic prostate cancer. (Funded by Medivation and Astellas Pharma; PREVAIL ClinicalTrials.gov number, NCT01212991.)

5.4.2.6 Terapia dopo docetaxel

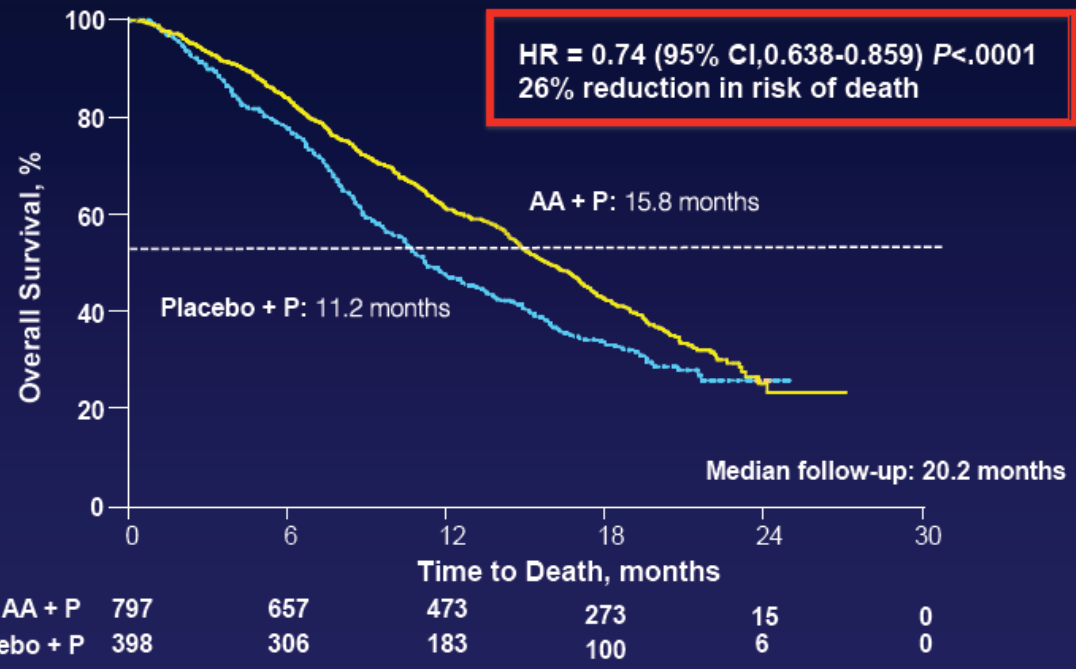
Nuovi farmaci ormonali

Chemioterapia di II linea

Qualità dell'evidenza SIGN	Raccomandazione	Forza della raccomandazione clinica
B	I pazienti con malattia metastatica, resistente alla castrazione, in progressione dopo una linea di trattamento con docetaxel, devono essere sottoposti a trattamento con uno dei nuovi farmaci la cui efficacia è stata dimostrata nell'ambito di studi clinici controllati e che, attualmente, sono registrati per questa indicazione (Abiraterone acetato, Cabazitaxel, Enzalutamide).	**Positiva forte**

COU-AA-301: Overall Survival

Second Preplanned Analysis
Median Benefit: 4.6 months



AA, abiraterone acetate; CI, confidence interval; P, prednisone

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

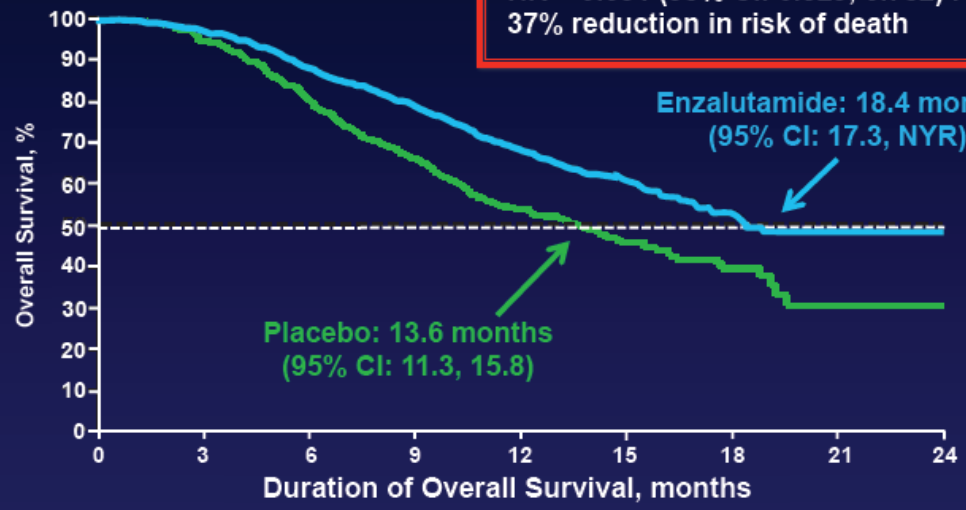
COU-AA-301: Tolerability

Adverse events	Abiraterone + prednisone (n = 791)		Placebo + prednisone (n = 394)	
Discontinuation due to an adverse event, %	13		18	
Death due to an adverse event, %	13		16	
Most common adverse events, n (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Fatigue	372 (47)	72 (9)	174 (44)	41 (10)
Back pain	262 (33)	56 (7)	141 (36)	40 (10)
Nausea	258 (33)	17 (2)	130 (33)	11 (3)
Arthralgia	239 (30)	40 (5)	95 (24)	17 (4)
Adverse events of special interest, n (%)				
Fluid retention and edema	261 (33)	20 (3)	94 (24)	4 (1)
Hypokalemia	143 (18)	35 (4)	36 (9)	3 (<1)
Hypertension	88 (11)	10 (1)	32 (8)	1 (<1)

Fizazi K, et al. *Lancet Oncol.* 2012;13(10):983-992. de Bono JS, et al. *N Engl J Med.* 2011;364(21):1995-2005.

AFFIRM Overall Survival: Median of 4.8 Months

HR = 0.631 (95% CI: 0.529, 0.752) *P* < .0001
37% reduction in risk of death



Enzalutamide	800	775	701	627	400	211	72	7	0
Placebo	399	376	317	263	167	81	33	3	0

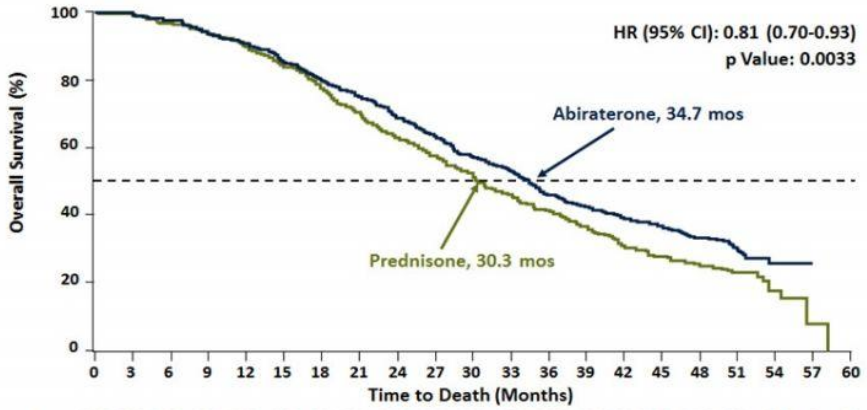
Scher HI, et al. *N Engl J Med.* 2012;367(13):1187-1197.

AFFIRM: Tolerability

Patients with adverse events, n (%)	Total events		Grade ≥ 3 events	
	Enzalutamide (n = 800)	Placebo (n = 399)	Enzalutamide (n = 800)	Placebo (n = 99)
Adverse events	785 (98)	390 (98)	362 (45)	212 (53)
Serious adverse events	268 (34)	154 (39)	227 (28)	134 (34)
Discontinuations due to adverse events	61 (8)	39 (10)	37 (5)	28 (7)
Adverse events leading to death	23 (3)	14 (4)	23 (3)	14 (4)
Adverse events of interest				
Fatigue	269 (34)	116 (29)	50 (6)	29 (7)
Cardiac disorders	49 (6)	30 (8)	7 (1)	8 (2)
Myocardial infarction	2 (<1)	2 (<1)	2 (<1)	2 (<1)
LFT abnormalities	8 (1)	6 (2)	3 (<1)	3 (<1)
Seizure	7 (<1)	0	7 (<1)	0

Scher HI, et al. *N Engl J Med.* 2012;367(13):1187-1197.

Study 302:
Final OS Analysis

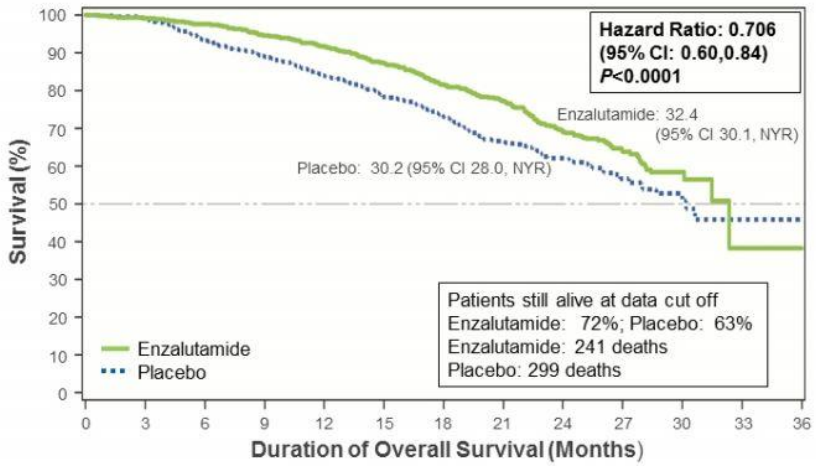


Abiraterone	546	538	525	504	483	453	422	394	359	330	296	273	235	218	202	189	118	59	15	0	0
Prednisone	542	534	509	493	466	438	401	363	322	292	261	227	201	176	148	132	84	42	10	1	0

- 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; Abstract 7530 (oral presentation)

PREVAIL Interim Analysis:
Enzalutamide Reduced Risk of Death by 29%



Patients at Risk													
Enzalutamide	872	863	850	824	797	745	566	395	244	128	33	2	0
Placebo	845	835	781	744	701	644	484	328	213	102	27	2	0

Median Follow-up 22 Months

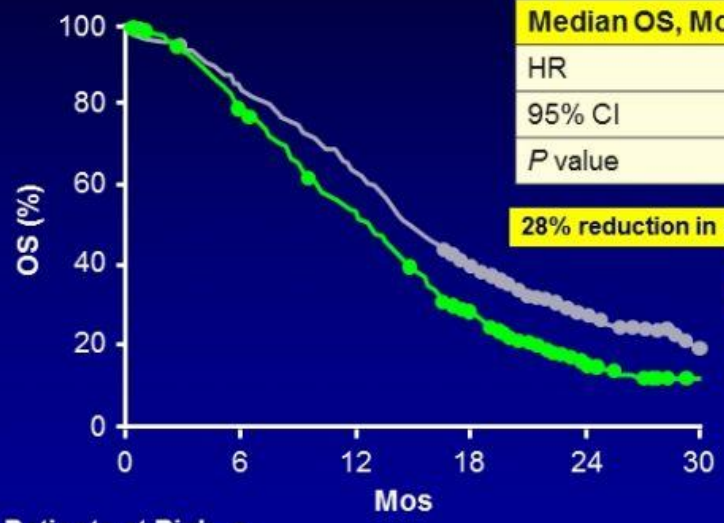
Beer et al, N Engl J Med. 2014; 371(5):424-33

TROPIC *Primary Endpoint:* OS
ITT Analysis

+2.4 m

De Bono JS, et al

	CBZ+P	M+P
Median OS, Mos	**15.1**	**12.7**
HR	0.70	
95% CI	0.59-0.83	
P value	< .0001	



28% reduction in risk of death

Censored
MP
CBZP

Combined median follow-up: 13.7 mos

30% risk reduction

Patients at Risk, n

MP	377	299	195	94	31	9
CBZP	378	321	241	137	60	19

28% of patients still alive at 2 years with cabazitaxel vs 17% with mitoxantrone

Cabazitaxel: Main Adverse Events

	MP (n=371)		CBZP (n=371)	
	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)
Any adverse event	88	39	96	57
Febrile neutropenia	1	1	8	8
Diarrhea	11	<1	47	6
Fatigue	27	3	37	5
Back pain	12	3	16	4
Nausea	23	<1	34	2

De Bono JS, et al. *Lancet.* 2010;376:1147-1154.

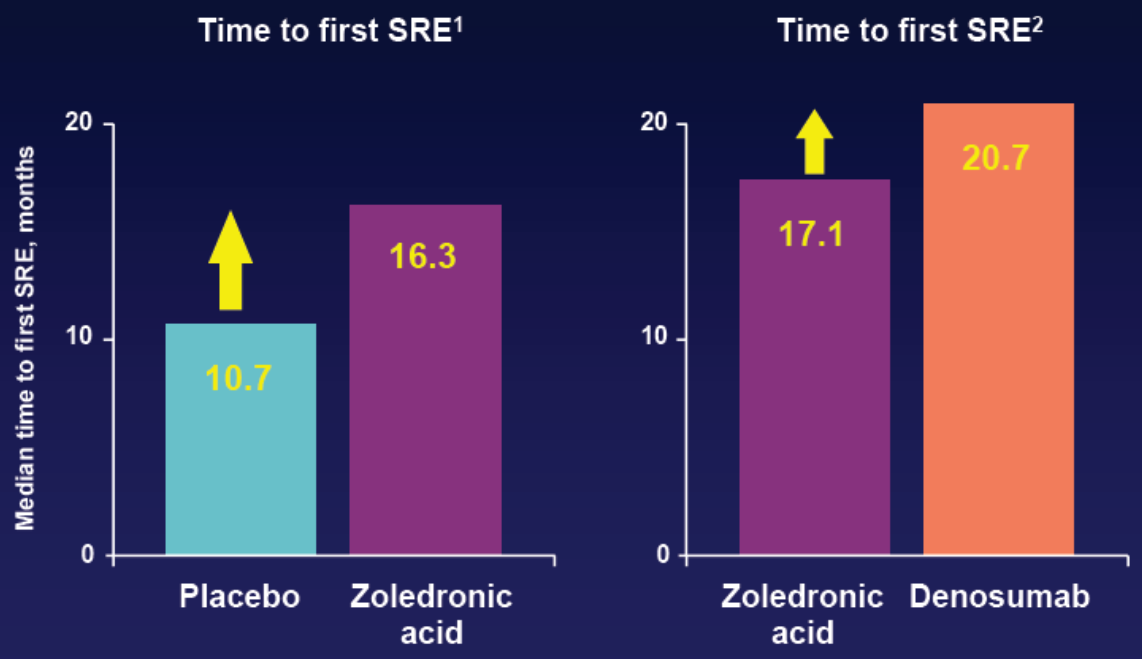
Medscape EDUCATION

5.4.3 Trattamento delle metastasi ossee

5.4.3.1 Terapia con difosfonati e inibitori di RANKL

Qualità dell'evidenza SIGN	Raccomandazione	Forza della raccomandazione clinica
B	In pazienti con evidenza di metastasi ossee può essere preso in considerazione un trattamento per la prevenzione degli eventi scheletrici con denosumab o con acido zoledronico.	**Positiva debole**

Incremental Benefit of SRE Prevention



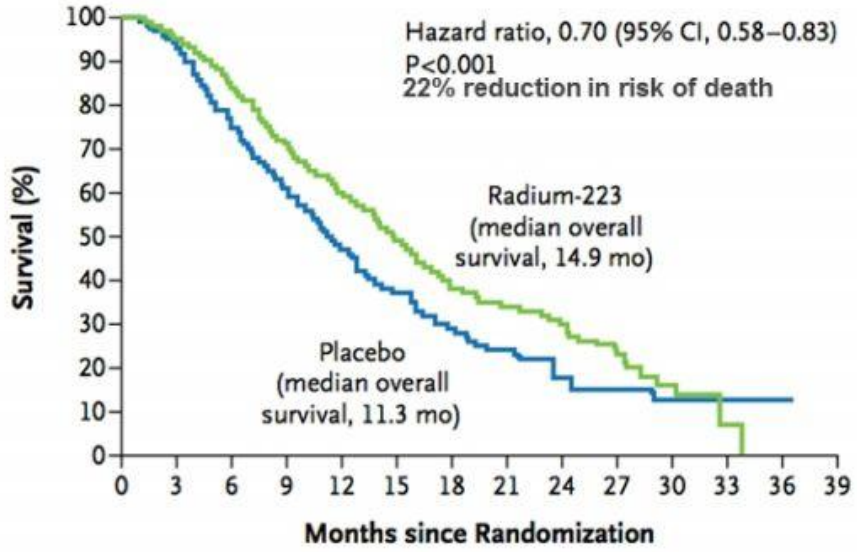
1. Saad F, et al. *J Natl Cancer Inst.* 2002;94(19):1458-1468. 2. Fizazi K, et al. *Lancet.* 2011;377(9768):813-822.

5.4.3 Trattamento delle metastasi ossee

5.4.3.3 Terapia radiometabolica

Qualità dell'evidenza SIGN	Raccomandazione	Forza della raccomandazione clinica
B	Radium-223 può essere considerato una delle opzioni terapeutiche disponibili nei pazienti resistenti alla castrazione con metastasi ossee sintomatiche e senza metastasi linfonodali o viscerali o concomitante progressione a livello prostatico (per i pazienti inizialmente sottoposti a RT definitiva) o a livello della loggia prostatica (nei pazienti sottoposti in precedenza a prostatectomia radicale).	**Positiva debole**

ALSYMPCA: Overall Survival
3.6 Month Improvement vs Placebo



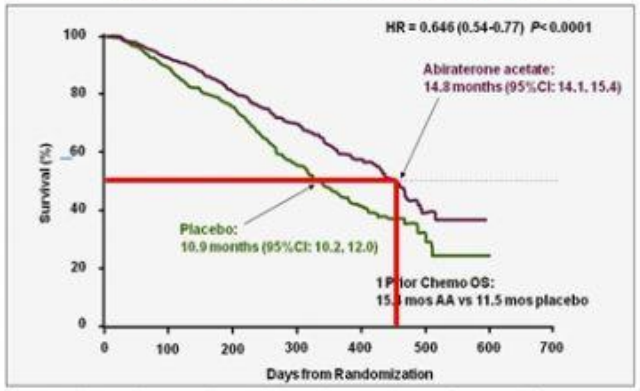
No. at Risk														
Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

Median Follow-up 36 months
Final analysis: radium-223 333/614 deaths;
placebo 195/307 deaths

Parker et al. N Eng J Med 2013; 369(3):213–23

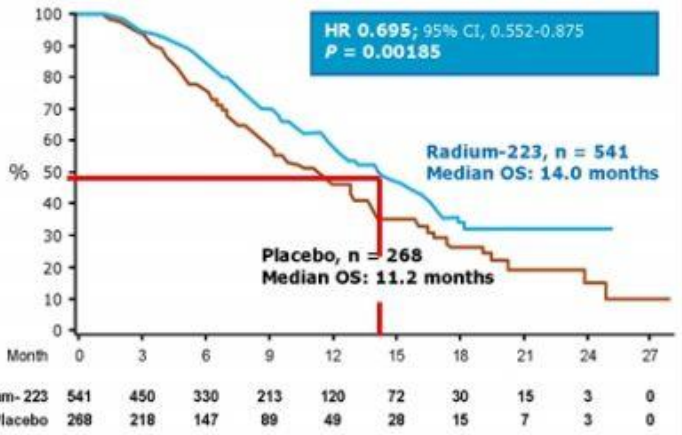
ESMO congress Milan 2010

COU-AA-301: Abiraterone Acetate Improves Overall Survival in mCRPC

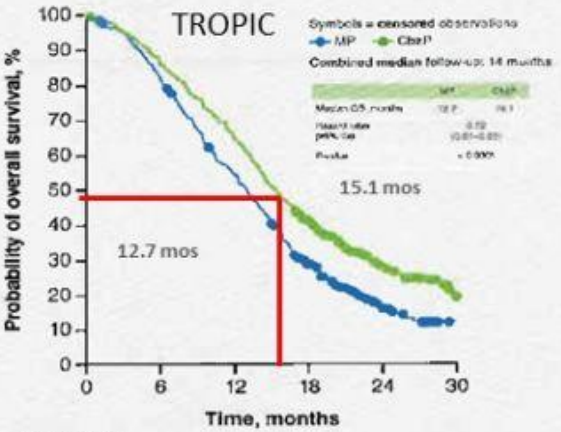


AA	797	728	631	475	204	25	0

ALSYMPCA Overall Survival

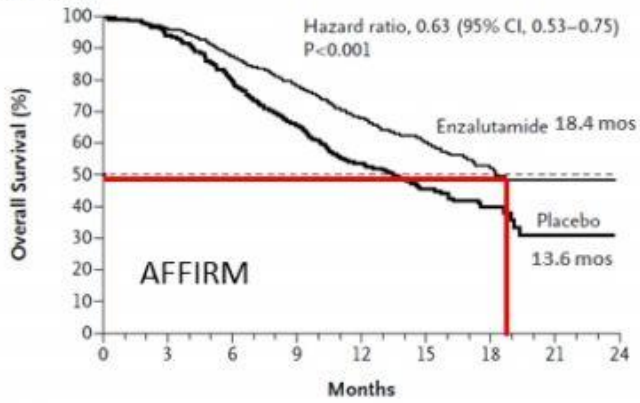


Radium-223	541	450	330	213	120	72	30	15	3	0
Placebo	268	218	147	89	49	28	15	7	3	0



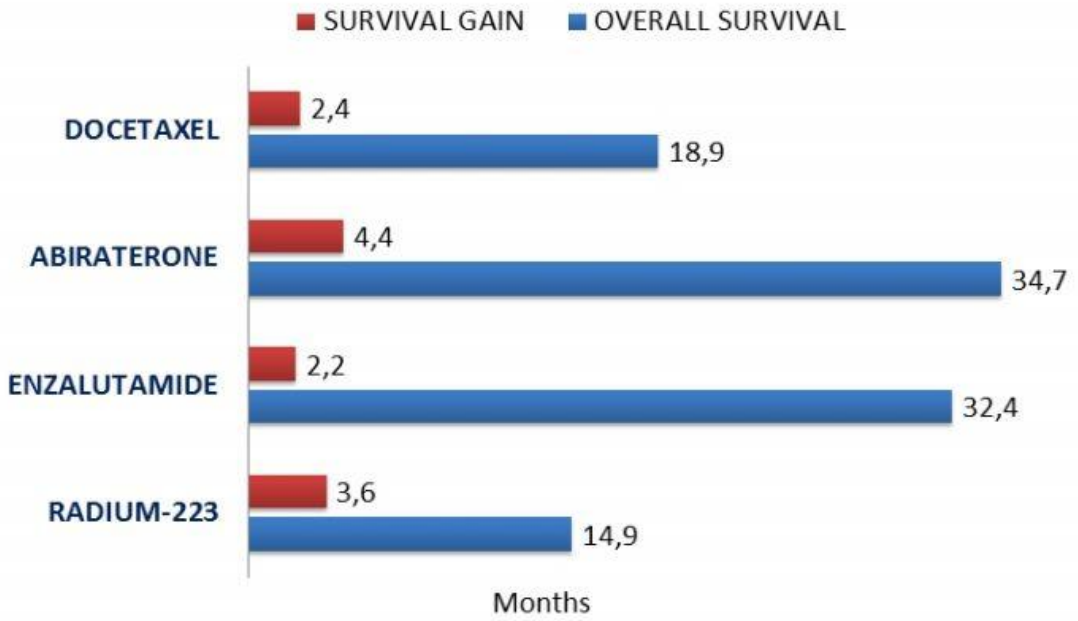
CbzP	378	321	241	137	69	19	
MP	377	299	195	94	31	9	

A Overall Survival



No. at Risk									
Enzalutamide	800	775	701	627	400	211	72	7	0
Placebo	399	376	317	263	167	81	33	3	0

Front-line options that improve survival

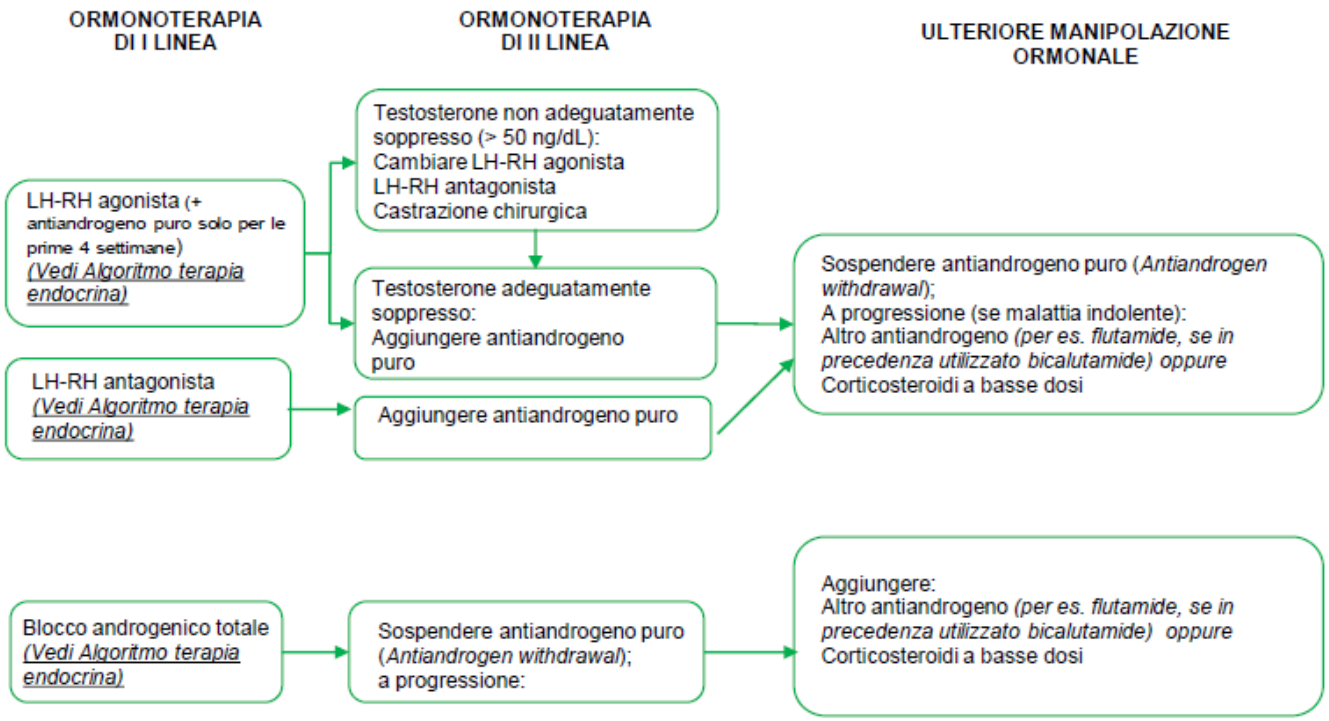


[1]Tannock et al. N Engl J Med. 2004
[2]Kantoff et al.N Engl J Med. 2010
[3]Ryan C et al. ESMO 2014; Abstract 7530 (oral presentation)
[4]Beer et al. N Engl J Med 2014
[5]Parker et al.N Engl J Med. 2013

"Price is what you pay. Value is what you get" (W. Buffett)

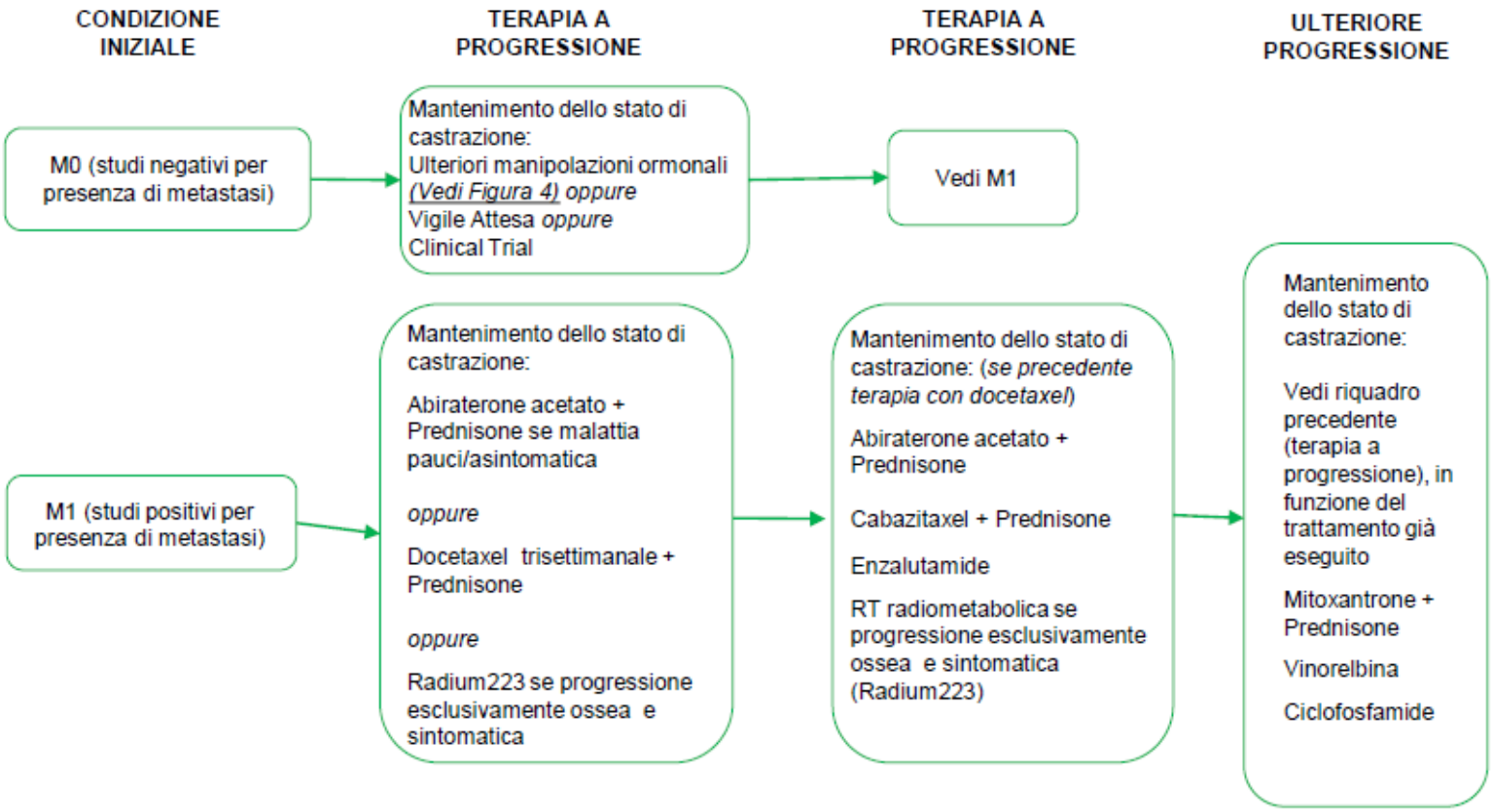
Drug	Dose/Route	AWS Cost per cycle - Drug Only	# of Cycles	Survival
Docetaxel	150 mg IV (75 mg/m2 x 2 m2)	$2921.20	Median: 6	Yes
Cabazitaxel	50 mg IV (25 mg/m2 x 2 m2)	$8408.08	Median :6	Yes
Abiraterone	1000 mg PO (30-day)	$8203.91	Median 8 ms	Yes
Enzalutamide	160 mg PO (30-day)	$9467.46	Median 8 ms	Yes
Sipuleucel-T	IV	$37,200	3 cycles	Yes
Radium-223	IV	$28,173	6 cycles	Yes
Denosumab	120 mg SC	$2017.68	Monthly	No
Zoledronic Acid	4 mg IV	$360 (generic) - $1196.56	Monthly	No

Figura 4 - Malattia ormonosensibile (M1)*



**In linea di principio, i pazienti M1a dovrebbero essere trattati come gli altri pazienti metastatici ovvero avviati a terapia endocrina secondo le modalità previste nella Figura. Tuttavia, pur in assenza di studi prospettici e tantomeno controllati, singoli "case report" e analisi di serie retrospettive indicano che in casi molto selezionati, con malattia linfonodale iuxta-regionale, che abbiano risposto in maniera adeguata alla terapia endocrina di prima linea, possa essere utilizzata in aggiunta anche la RT esterna, eventualmente con "boost" sulle sedi di malattia, in analogia a quanto avviene per i tumori extra-prostatici cN1*

Figura 5 - Malattia resistente alla castrazione (CRPC) (M0/M1)



Guidelines on

Prostate Cancer