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NUOVE PROSPETTIVE DI CURA PER IL PAZIENTE CON CARCINOMA PROSTATICO AVANZATO

22-23 NOVEMBRE 2018

MILANO

HILTON MILAN
via L. Galvani 12

SIU
Società Italiana di Urologia
dal 1908

Thermocline Otto Dix, oil on canvas 2017
A. Annino

La malattia metastatica resistente alla castrazione

Dr. Luca Cindolo

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PER IL PAZIENTE CON
CARCINOMA PROSTATICO AVANZATO

Quando trattare?

Trattare o non trattare?

Quale farmaco?

Neoplasia prostatica

Terapia ormonale

Sviluppo M0 CRPC

Progressione a M1 CRPC

Decisione terapeutica


JOURNAL OF CLINICAL ONCOLOGY | SPECIAL ARTICLE

Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3

Come seguire il paziente?

Quando lo shift?

Non è meglio l'invio all'oncologo?

Quando sospendere?

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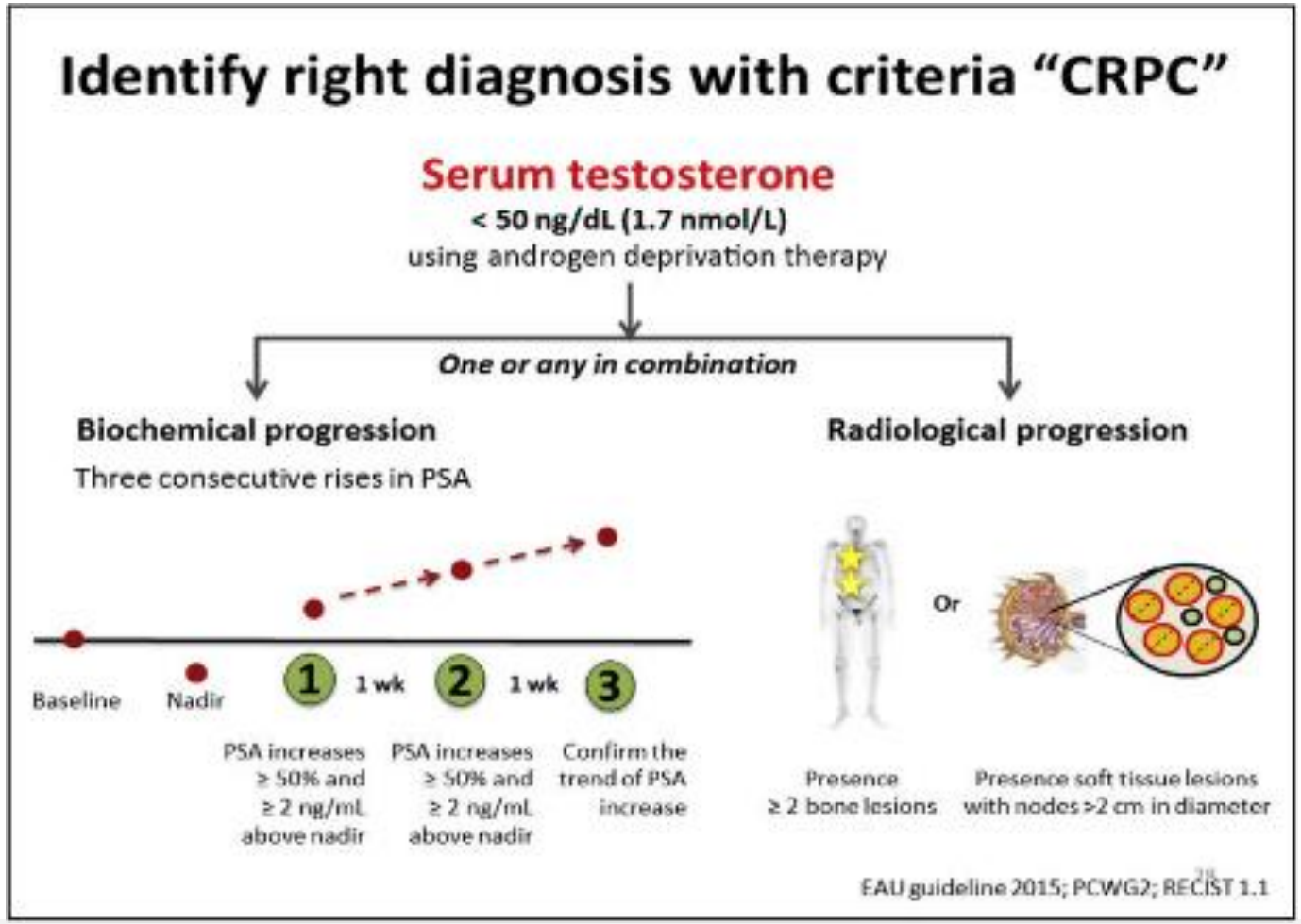
definizioni

Definizione



Varietà quadri clinici
Sviluppo di lesioni ossee 90%

eventi scheletrici

mCRPC basso volume, asintomatici, ottima QoL

mCRPC alto volume, alto rischio, sintomi rilevanti e significativi (dolore)

mCRPC rapidamente progressivi, alto volume

«...aim of therapy in patients with mCRPC is to match the appropriate strength therapy to the appropriate level of patient symptoms and disease burden». Ryan JC 2018

ELSEVIER

UROLOGIC ONCOLOGY

Urologic Oncology: Seminars and Original Investigations 35 (2017) S1–S13

Original article

Navigating the evolving therapeutic landscape in advanced prostate cancer

E. David Crawford, M.D.[a], Daniel Petrylak, M.D.[b,c], Oliver Sartor, M.D.[d,e,*]

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mCRPC Treatment: The Right Treatment for the Right Patient at the Right Time: EVERYDAY UROLOGY- Full Text Article

Everyday Urology-Oncology Insights: Volume 1, Issue 4

EURURO-7792; No. of Pages 12

ARTICLE IN PRESS

EUROPEAN UROLOGY XXX (2018) XXX–XXX

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journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Prostate Cancer

Editorial by XXX on pp. x–y of this issue

Update on Systemic Prostate Cancer Therapies: Management of Metastatic Castration-resistant Prostate Cancer in the Era of Precision Oncology

Philipp Nuhn[a], Johann S. De Bono[b], Karim Fizazi[c], Stephen J. Freedland[d,e], Maurizio Grilli[f], Philip W. Kantoff[g], Guru Sonpavde[h], Cora N. Sternberg[i], Srinivasan Yegnasubramanian[j,k], Emmanuel S. Antonarakis[j,k,]*

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Online version at http://www.minervamedica.it

Minerva Urologica e Nefrologica 2018 February;70(1):22-41
DOI: 10.23736/S0393-2249.17.02976-9

REVIEW

Castration-resistance prostate cancer: what is in the pipeline?

Cosimo DE NUNZIO[1,*], Fabrizio PRESICCE[1], Silvana GIACINTI[2], Maria BASSANELLI[2,3], Andrea TUBARO[1]

Our challenge in the near future will be to identify the right treatment or better the right combination and sequencing of treatments that should be used to manage patients with CRPC or even with advanced prostate cancer.

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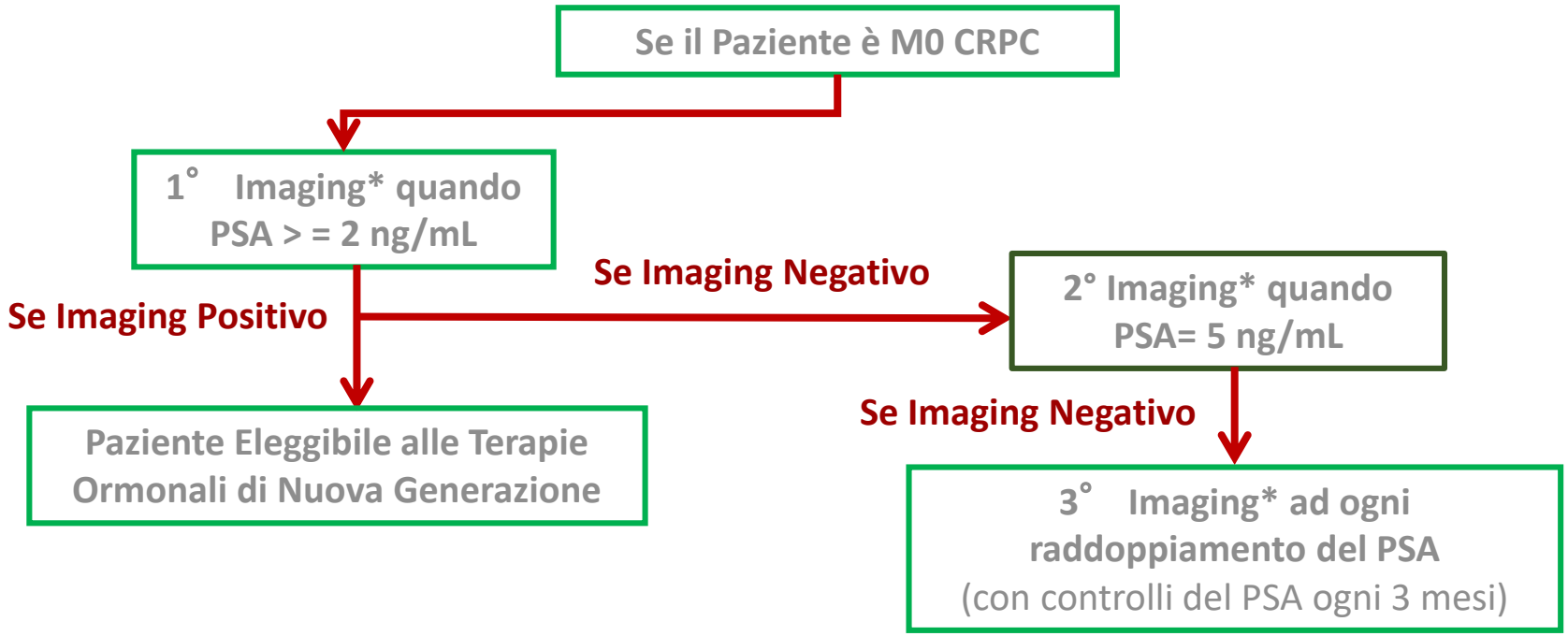
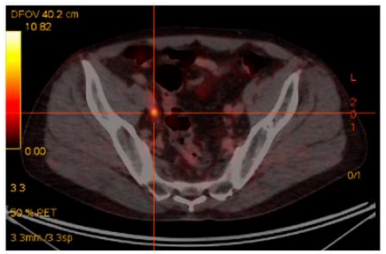
EAU Guidelines
Il Metodo RADAR



*Preferibilmente Scintigrafia + TAC oppure Whole Body MRI oppure PET

Crawford et al, UROLOGY 2014
Linee guida EAU 2015



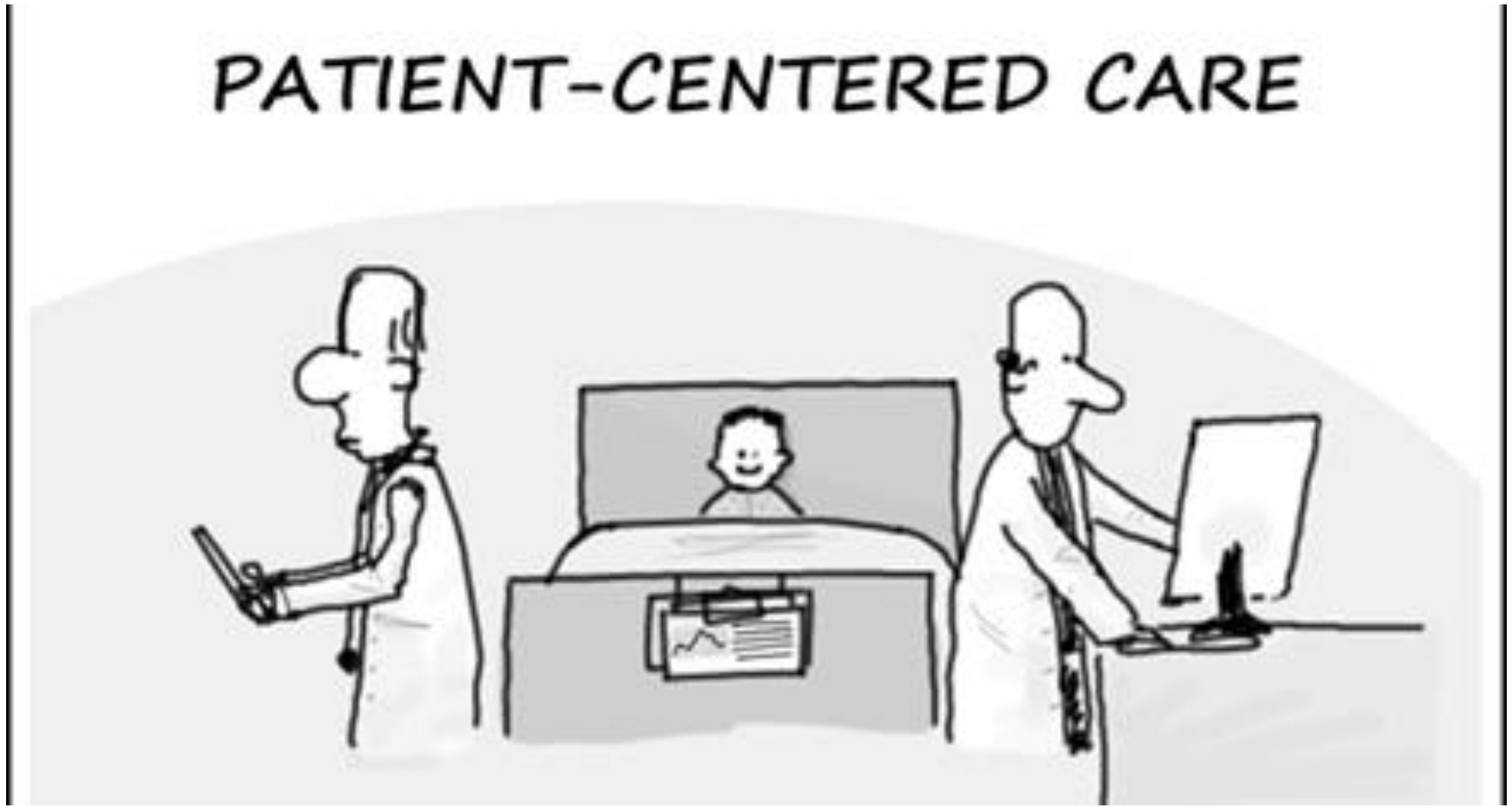
	Newly Diagnosed Patients	Biochemical Recurrent Patients	M0 Castrate-Resistant Patients	M1 Castrate-Resistant Patients*
RADAR I Conventional Scan Recommendations	Conventional scan high- and intermediate-risk patient with at least 2 of the following criteria positive: • PSA level >10 ng/ml • Gleason score ⩾7 • Palpable disease (⩾T2b)	1st conventional scan when PSA level between 5 and 10 ng/ml Imaging frequency if negative for previous conventional scan: 2nd scanning when PSA=20 ng/ml and every doubling of PSA level thereafter (based on PSA testing every 3 months)	1st conventional scan when PSA level ⩾2 ng/ml Imaging frequency if negative for previous conventional scan: 2nd conventional scan when PSA=5 ng/ml and every doubling of PSA level thereafter (based on PSA testing every 3 months)	Utilize conventional scans, and consider NGI only if conventional scans are negative and the clinician still suspects disease progression NGI based on at least one of the following: • With every doubling of PSA since the previous image • Every 6–9 months in the absence of PSA rise • Change in symptomatology • Change in performance status
RADAR III NGI Recommendations	If conventional imaging is equivocal or negative with continued high suspicion for metastatic disease, consider NGI	Consider NGI for PSA ⩾0.5 PSA <0.5 can be considered based on specific performance of various NGI techniques	Only consider NGI in the setting of PSADT <6 months, when M1 therapies would be appropriate	

*Limitations include lack of data and difficulty making comparisons to non-NGI techniques.

NGI, next generation imaging; M, metastasis; PET, positron-emission tomography; PSA, prostate-specific antigen; PSADT, PSA doubling time; RADAR, Radiographic Assessments for Detection of Advanced Recurrence; T, tumour

Crawford ED, et al. J Urol. 2018

pazienti



The term “patient-centred” has been first used in a paper by Enid Balint in 1969 to indicate that the ‘whole person’ has to be considered in the clinical consultations.

De Nunzio et al. BMC Urology 2018

European Association of Urology

NICE National Institute for Health and Care Excellence

Improvement of clinical outcomes and drug adherence

Unfortunately, in the field of urology the use of this approach is still very limited.

De Nunzio et al. BMC Urology 2018

PCWG3 recognizes the importance of patient-centered drug development and reporting the patient experience on study

Riconoscere l'importanza della **prospettiva** del paziente e della necessità di seguire il paziente con analisi, questionari, imaging

Misurare i sintomi correlati con la malattia includendo **dolore**, **interferenze** della malattia sulla vita, funzioni **fisiche**

Controllare durante la terapia la presenza o comparsa di eventi **avversi** in maniera rigorosa

Scher HI, et al, JCO 2016

7 regole d'oro per una comunicazione migliore

1) Crea la relazione medico-paziente;
2) Apri la discussione;
3) Raccogli informazioni;

Prescrivi e programma controllo

De Nunzio et al. BMC Urology 2018

Limitazioni di cibo... Poco rilevanti!

Clinical Therapeutics/Volume 39, Number 4, 2017

Patients' Preferences for the Treatment of Metastatic Castrate-resistant Prostate Cancer: A Discrete Choice Experiment

Lina Eliasson, PhD[1]; Hayley M. de Freitas, MSc[1]; Lindsay Dearden, MSc[2]; Brian Calimlim, DrPH[3]; and Andrew J. Lloyd, DPhil[1]

(N = 285)

Completo controllo del dolore

OR,12.069 [95% CI, 10.555–13.800])

Trattamenti che ritardano la chemio

OR, 1.727 [95% CI, 1.548–1.927])

Trattamenti che compromettono meno memoria e funzioni cognitive

OR, 2.115 [95% CI, 1.849–2.420]

Trattamenti che hanno basso rischio di fatigue

OR, 1.365 [95% CI 1.219-1.528]

Trattamenti con minori accessi ospedalieri

OR, 1.245 [95% CI 1.111-1.397]

A prospective real life study evaluating Abiraterone Acetate plus Prednisone (AAP) for metastatic Castration Resistant Prostate Cancer (mCRPC) (Abitude Study)

A. Sciarra[1], M. Scarcia[2]; L. Cindolo[3], P. Verze[4], S.Salciccia[1], G. Ludovico[2], P.Castellan[3]; M. Battaglia[5], G. Carrieri[6], V. Cicalese[7], A. De Lisa[8], F. Uricchio[9], L. Livi[10], D. Santini[11], G.Procopio[12], P. Beccaglia[13], M. Gallucci[14], and V. Mirone[4].

Abiraterone permette il controllo del dolore nei pazienti mCRPC trattati in post ADT

Pain assessment – BPI questionnaire results

	N	25th percentile	Median	75th percentile
Worst pain intensity				
Baseline	388	0.0	2.0	4.0
6-month f-up	272	0.0	1.0	4.0

✓Abiraterone già dopo 6 mesi di trattamento dimezza l'intensità del più elevato dolore provato dai pazienti

Patient's Quality of Life – EQ-5D-3L questionnaire results

		Baseline (N=453)	6 months (N=453)
Pain/ Discomfort	I have no pain or discomfort	235 (53.4%)	202 (62.9%)
	I have moderate pain or discomfort	197 (44.8%)	114 (35.5%)
	I have extreme pain or discomfort	8 (1.8%)	5 (1.6%)
	missing	13	132

✓Abiraterone migliora il dolore anche nei pazienti che al basale erano già sintomatici

Note. Percentages were calculated over number of patients with non-missing response.

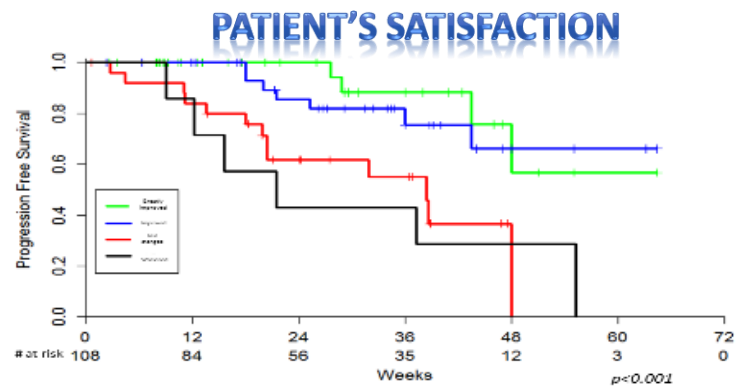
Sciarra A. et al. Eur Urol Suppl 2018

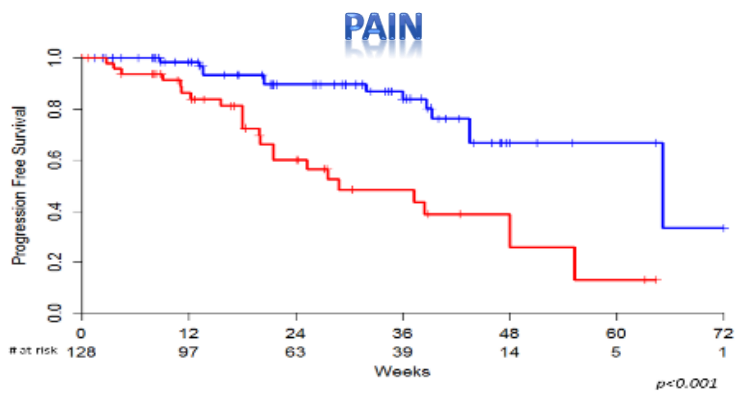
LA PATIENTS' SATISFACTION CON ABIRATERONE È RISULTATA "MOLTO MIGLIORATA" NEL 36,1% DEI PAZIENTI E "MIGLIORATA" NEL 32,4% DEI PAZIENTI.

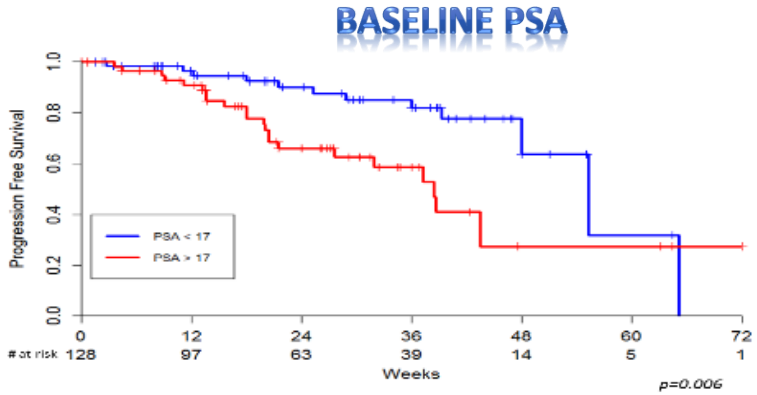
Caratteristiche demografiche e patologiche dei pazienti al basale

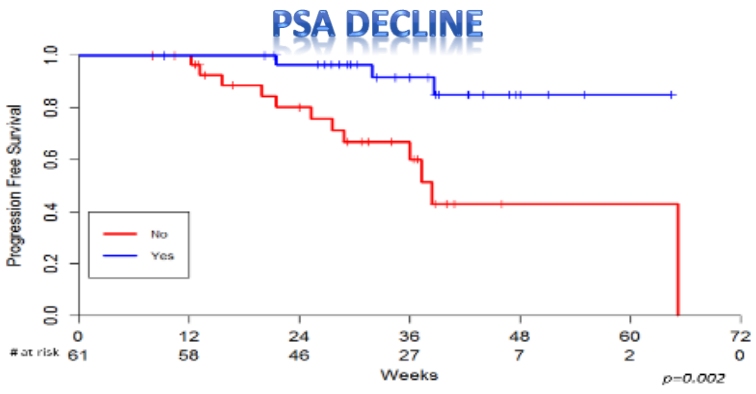
Caratteristiche	Valore
Età media (SD), anni	76,7 (7,1)
ECOG Performance Status, n (%)	
0-1	119 (93)
>2	9 (7)
ALT mediana al basale (range), U/L	20 (8-87)
AST mediano al basale (range), U/L	18,5 (6-309)
Comorbidità, n (%)	
Nessuna	26 (20)
Solo cardiovascolari	47 (36,4)
Solo metaboliche	11 (8)
Solo neurologiche	4 (3)
Solo neoplasia pregressa	1 (0,7)
Multiple	26 (20)
Altro	14 (11,9)

Tabella 1 di Rif.5
Abbreviazioni: ALT = alanina aminotransferasi;
AST = Aspartato aminotransferasi;
ECOG = Eastern Cooperative Oncology Group









La *Patient's Satisfaction e il dolore* sono predittori di PFS

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Cindolo L et al. Clinical Genitourinary Cancer 2017

terapie

Semin Oncol. 2018 Oct 30. pii: S0093-7754(17)30050-7. doi: 10.1053/j.seminoncol.2018.10.001. [Epub ahead of print]

Current therapeutic options in metastatic castration-resistant prostate cancer.

Ingrosso G[1], Detti B[2], Scartoni D[3], Lancia A[1], Giacomelli I[3], Baki M[3], Carta G[3], Livi L[3], Santoni R[1].

⊕ Author information

Abstract

BACKGROUND: The tumors of many patients with prostate cancer eventually become refractory to androgen deprivation therapy with progression to metastatic castration-resistant disease. Significant advances in the treatment of metastatic castration-resistant prostate cance (mCRPC) have been made in recent years, and new treatment strategies have recently been made available. The aim of this report was to schematically review all the approved pharmacologic treatment options for patients with mCRPC through 2018, analyzing the efficacy and possible side effects of each therapy to assist clinicians in reaching an appropriate treatment decision. New biomarkers potentially of aid in the choice of treatment in this setting are also briefly reviewed.

METHODS: We performed a literature search of clinical trials of new drugs and treatments for patients diagnosed with mCRPC published through 2018.

RESULTS: Two new hormonal drugs, abiraterone acetate and enzalutamide have been approved by FDA in 2011 and 2012, respectively for the treatment of patients with mCRPC and have undergone extensive testing. While these treatments have shown a benefit in progression-free and overall survival, the appropriate sequencing must still be determined so that treatment decisions can be made based on their specific clinical profile. Cabazitaxel has been shown to be an efficient therapeutic option in a postdocetaxel setting, while its role in chemotherapy-naïve patients must still be determined. Sipuleucel-T and radium-223 have been studied in patients without visceral metastases and have achieved overall survival benefits with good safety profiles. The feasibility and efficacy of combinations of new treatments with other known therapies such as chemotherapy are currently under investigation.

CONCLUSIONS: Drug development efforts continue to attempt to prolong survival and improve quality of life in the mCRPC setting, with several therapeutic options available. Ongoing and future trials are needed to further assess the efficacy and safety of these new drugs and their interactions, along with the most appropriate sequencing.

EURURO-7792; No. of Pages 12
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EUROPEAN UROLOGY XXX (2018) XXX–XXX

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Update on Systemic Prostate Cancer Therapies: Management of Metastatic Castration-resistant Prostate Cancer in the Era of Precision Oncology

Philipp Nuhn [a], Johann S. De Bono [b], Karim Fizazi [c], Stephen J. Freedland [d,e], Maurizio Grilli [f], Philip W. Kantoff [g], Guru Sonpavde [h], Cora N. Sternberg [i], Srinivasan Yegnasubramanian [j,k], Emmanuel S. Antonarakis [j,k,]*

Table 1 – Current therapies in mCRPC

AR-targeted therapy		
Abiraterone	CYP17A1 inhibitor	Approved
Enzalutamide	AR antagonist	Approved
Orteronel (TAK-700)	CYP17A1 inhibitor	Under clinical evaluation
Seviteronel (VT-464)	CYP17A1 inhibitor	Under clinical evaluation
Apalutamide (ARN-509)	AR antagonist	Under clinical evaluation
Darolutamide (ODM-201)	AR antagonist	Under clinical evaluation
Chemotherapy		
Docetaxel	Taxane	Approved
Cabazitaxel	Taxane	Approved
Immunotherapy		
Sipuleucel-T	Therapeutic vaccine	Approved
PROSTVAC-VF	Therapeutic vaccine	Under clinical evaluation
Ipilimumab (MDX-010)	CTLA-4 inhibitor	Under clinical evaluation
Nivolumab	PD-1 inhibitor	Under clinical evaluation
Pembrolizumab	PD-1 inhibitor	Under clinical evaluation
Atezolizumab	PD-L1 inhibitor	Under clinical evaluation
Avelumab	PD-L1 inhibitor	Under clinical evaluation
Bone-targeted therapy		
Bisphosphonates		Approved
Denosumab	RANKL inhibitor	Approved
Radium-223	Radionuclide	Approved
PARP inhibitors		
Olaparib	PARP inhibitor	Under clinical evaluation
Veliparib	PARP inhibitor	Under clinical evaluation
Rucaparib	PARP inhibitor	Under clinical evaluation
Niraparib	PARP inhibitor	Under clinical evaluation
Talazoparib	PARP inhibitor	Under clinical evaluation
Other emerging therapies and novel therapeutic targets		
Selinexor	XPO-1 inhibitor	Under clinical evaluation
SM88	Agent combination	Under clinical evaluation
Cabozantinib	Tyrosine kinase inhibitor	Under clinical evaluation
Tasquinimod	Small-molecule inhibitor	Negative
^{177}Lu-PSMA-617	PSMA-targeted therapies	Under clinical evaluation

Treatment	Trial	Reference	Survival (mos)	Survival gain (mos)
Docetaxel/prednisone vs mitoxantrone/predn.	TAX-327[1]	Tannock 2004	18.9 vs 16.5	**2,4**
Sipuleucel vs placebo		Kantoff 2010	25.8 vs 21.7	**4.1**
Abiraterone/prednisone vs Placebo/prednisone	COU-AA-302[3]	Ryan 2014	34.7 vs 30.3	**4,4**
Enzalutamide vs placebo	PREVAIL[4]	Beer 2014	35.3 vs 31.3	**4,0**
Radium-223 vs placebo/BSC	ALSYMPCA[5]	Parker 2013	14.9 vs 11.3	**3,6**

[1]Tannock et al. N Engl J Med. 2004 ; [2]Kantoff et al.N Engl J Med. 2010; [3]Ryan C et al. Lancet Oncol.2015
[4]Beer et al. European Urology 2016; [5]Parker et al.N Engl J Med. 2013

Esperienza italiana ABI

Safety and efficacy of abiraterone acetate in chemotherapy-naive patients with metastatic castration-resistant prostate cancer: an Italian multicenter "real life" study

Luca Cindolo, Clara Natoli, Cosimo De Nunzio, Michele De Tursi, Maurizio Valeriani, Silvana Giacinti, Salvatore Micali, Mino Rizzo, Giampaolo Bianchi, Eugenio Martorana, Marcello Scarcia, Giuseppe Mario Ludovico, Pierluigi Bove, Anastasia Laudisi, Oscar Selvaggio, Giuseppe Carrieri, Maida Bada, Pietro Castellan, Stefano Boccasile, Pasquale Ditonno, Paolo Chiodini, Paolo Verze, Vincenzo Mirone and Luigi Schips

BMC Cancer 2017 **17**:753
https://doi.org/10.1186/s12885-017-3755-x
Received: 13 January 2017 | **Accepted:** 6 November 2017 | **Published:** 10 November 2017

Discussion

In the current study, we have depicted a representative snapshot regarding the efficacy of AA in an unselected patient population as in a “real life” scenario. Herein, with a mid term follow-up, we confirmed that AA plus prednisone is an effective treatment with excellent patient satisfaction (“greatly improved/improved”: 69.2%) and with a good safety profile (Grade 3 and 4 toxicity recorded in 11.7%). However, in a different setting (real life vs RCT) of different mCRPC patients (older patients, with lower value of baseline PSA, and shorter follow-up) we obtained results in terms of survival outcomes comparable with those reported in the COU-302 trial [6]. In particular, we observed a median

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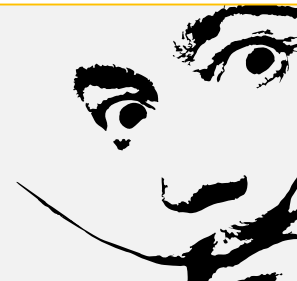
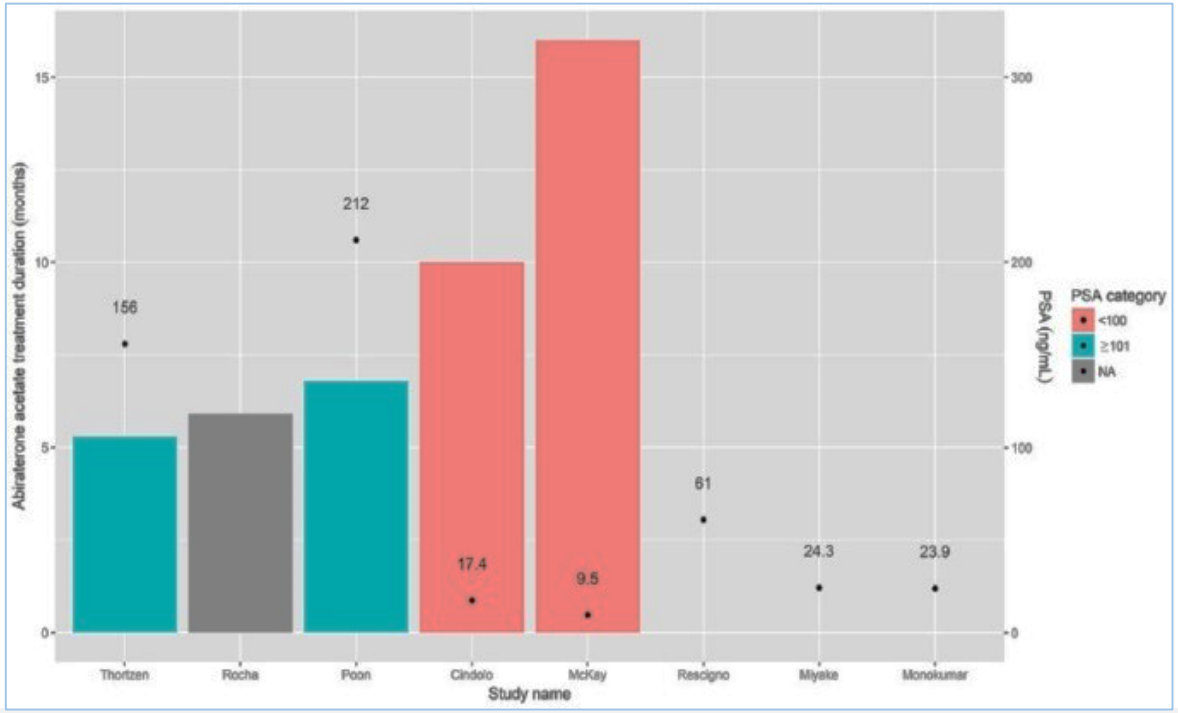


Therapeutic Advances in Urology — Systematic Review

Abiraterone in chemotherapy-naive patients with metastatic castration-resistant prostate cancer: a systematic review of 'real-life' studies

Ther Adv Urol
2018, Vol. 10(10) 305–315
DOI: 10.1177/1756287218786160

Michele Marchioni, Petros Sountoulides, Maida Bada, Sebastiano Rapisarda, Cosimo De Nunzio, Fabiola Raffaella Tamburro, Luigi Schips and Luca Cindolo



Revisione letteratura real life ABI

8 studi - 801 pazienti
PSA tra 9.5 e 212.0 ng/ml
Terapia con AA più lunga se PSA più basso

OS tra 14 e 36.4 mesi
% Tossicità ≥G3 tra 4.4 e 15.5%

Alta eterogeneità dei pazienti trattati
AA assicura buoni risultati sopravvivenza in setting 'real-life' setting

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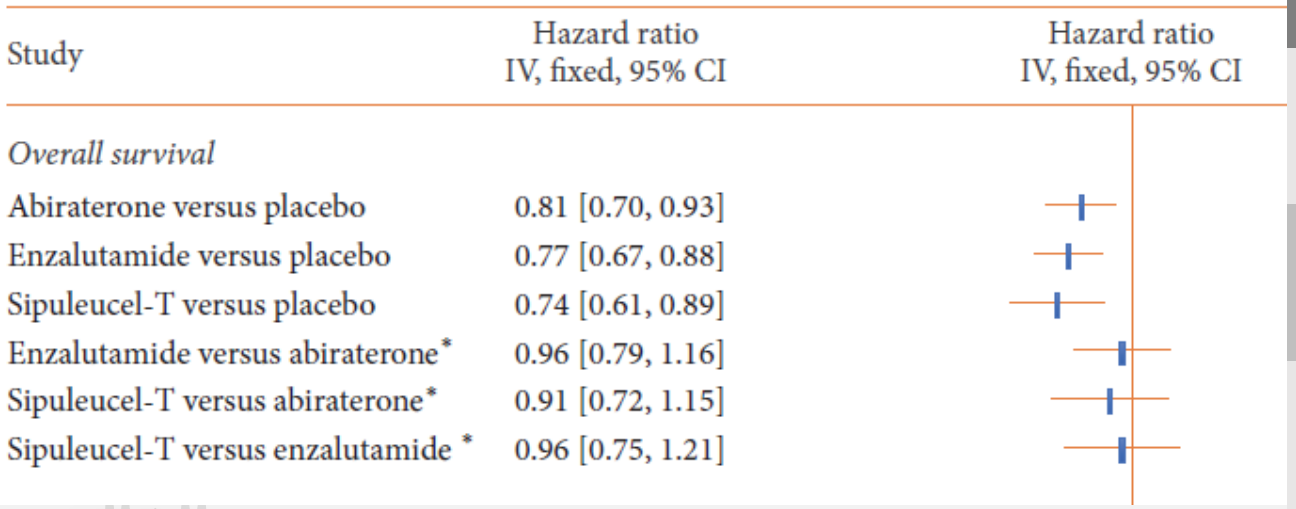
Quale scelta terapeutica nelle mani dell'urologo ?

BioMed Research International
Volume 2017, Article ID 3941217, 10 pages
https://doi.org/10.1155/2017/3941217

Review Article

Safety and Efficacy of First-Line Treatments for Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Indirect Comparison

Haofeng Zheng, Jialiang Chen, Wenhan Qiu, Sijie Lin, Yanxiong Chen, Guancan Liang, and Youqiang Fang



	COU-AA-302 (n = 542) %	PREVAIL (n = 871) %
Any adverse event	99	98
Any serious adverse event	33	34
Discontinuation owing to adverse event	10	8
Adverse event leading to death	4	3

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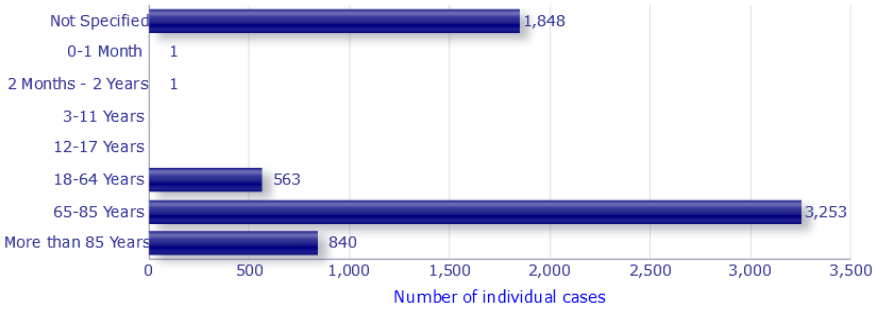
Number of individual cases identified by Age Group in EudraVigilance for Zytiga is 6.506

The number of individual cases identified in EudraVigilance for **ZYTIGA** is **6,506** (up to Sep 2018)

Number of individual cases by Age Group

Age Group	Cases	%
Not Specified	1,848	28.4%
0-1 Month	1	0.0%
2 Months - 2 Years	1	0.0%
3-11 Years	0	
12-17 Years	0	
18-64 Years	563	8.7%
65-85 Years	3,253	50.0%
More than 85 Years	840	12.9%
Total	**6,506**	**100.0%**

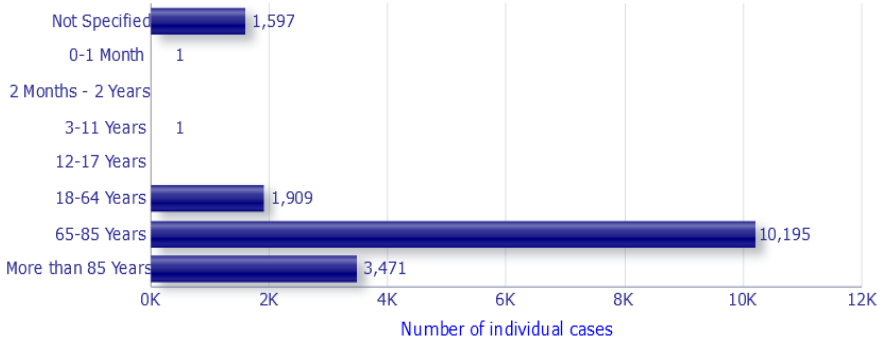


Number of individual cases identified by Age Group in EudraVigilance for Xtandi is 17.174

The number of individual cases identified in EudraVigilance for **XTANDI** is **17,174** (up to Sep 2018)

Number of individual cases by Age Group

Age Group	Cases	%
Not Specified	1,597	9.3%
0-1 Month	1	0.0%
2 Months - 2 Years	0	
3-11 Years	1	0.0%
12-17 Years	0	
18-64 Years	1,909	11.1%
65-85 Years	10,195	59.4%
More than 85 Years	3,471	20.2%
Total	**17,174**	**100.0%**



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EudraVigilance

Banca dati europea delle segnalazioni di sospette reazioni avverse ai farmaci

Settembre 2018

www.adrreports.eu/it/eudravigilance.html

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PER IL PAZIENTE CON
CARCINOMA PROSTATICO AVANZATO

Messaggi conclusivi

La ADT deve essere continuata

Tutte le nuove molecole sono
-efficaci e sicure
-pre e postchemio

Non esiste una sequenza corretta
-la scelta dipende da più fattori

Coltivare studio e la comprensione del CRPC

Dipanare paure circa incurabilità

Valutare le attese e misurare i sintomi

Ritardare progressione e dolore

Integrare con altri specialisti