Il paziente candidabile a trattamento con Radium 223 e la salute dell'osso

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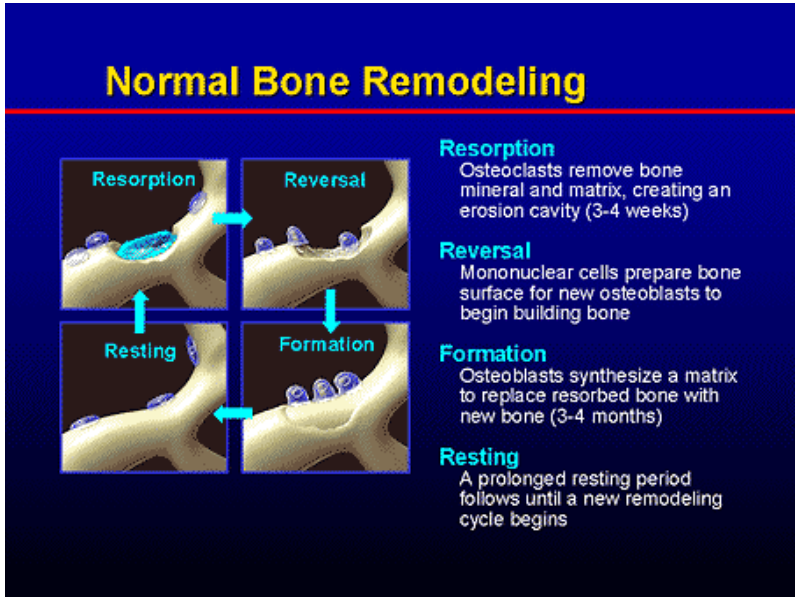
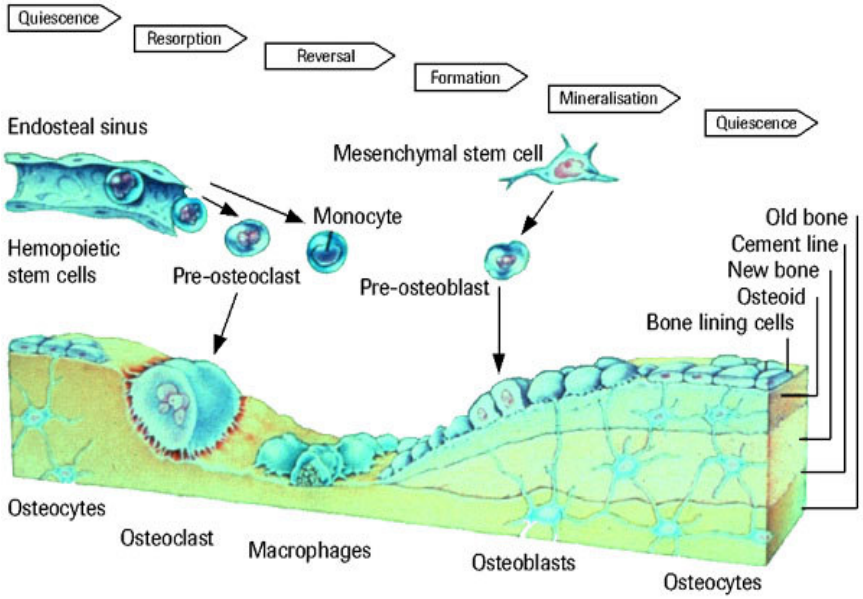
Brescia

Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili

Bone remodeling

REMODELING involves the removal of discrete packets of old bone ,replacement of these packets with newly synthesised protenaceous matrix and subsequent mineralization of the matrixto form new bone . (fernandez –tresguerres –hernandez et.al 2006)





Funzione del remodeling

Il rimodellamento osseo consente un continuo riassemblaggio della struttura e della massa ossea sostituendo tessuto vecchio con tessuto nuovo che viene successivamente mineralizzato

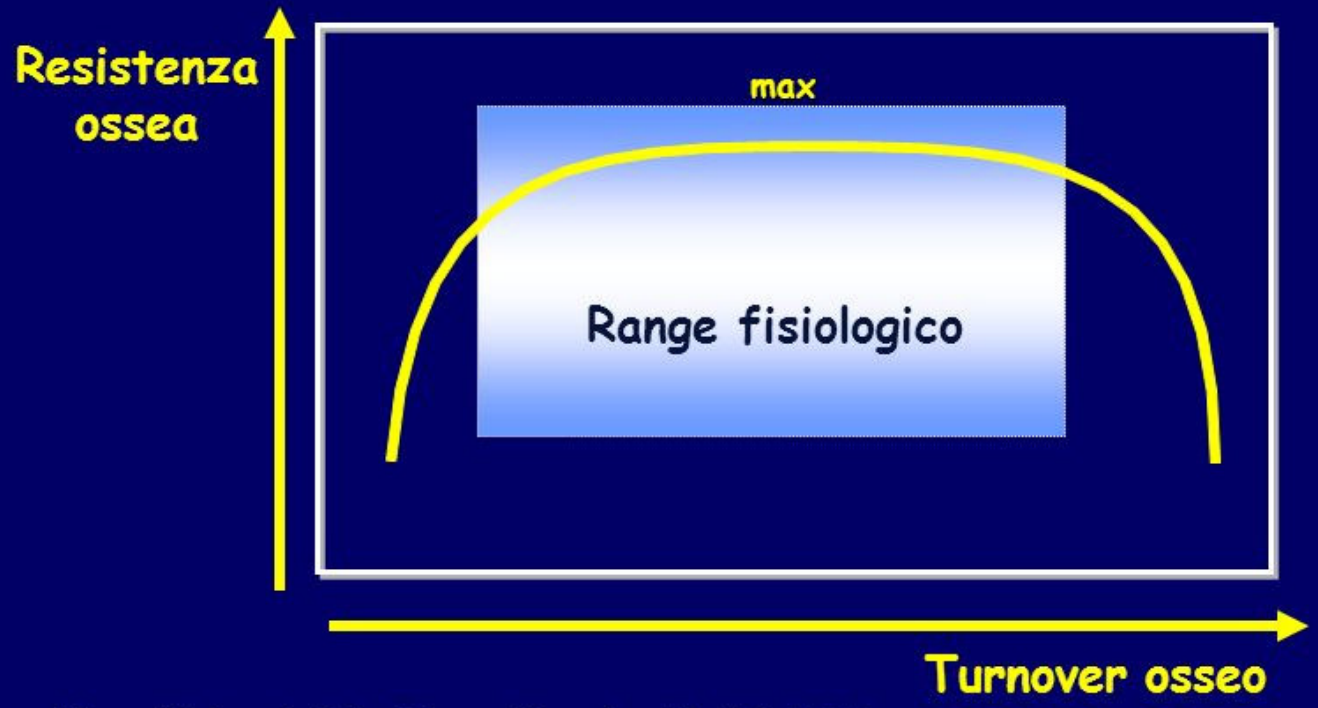
Il rimodellamento osseo comincia con il riassorbimento, operato dagli osteoclasti seguito dalla neoformazione operata dagli osteoblasti

Il rimodellamento
è finalizzato a mantenere la resistenza dell'osso rimuovendo i microdanni

Remodeling ottimale = massima resistenza

Turnover insufficiente
- Accumulo microdanni
- aumentata fragilità da eccessiva mineralizzazione

Turnover eccessivo
- aumento degli stress risers (zone deboli)
- aumento delle perforazioni
- perdita di connettività trabecolare

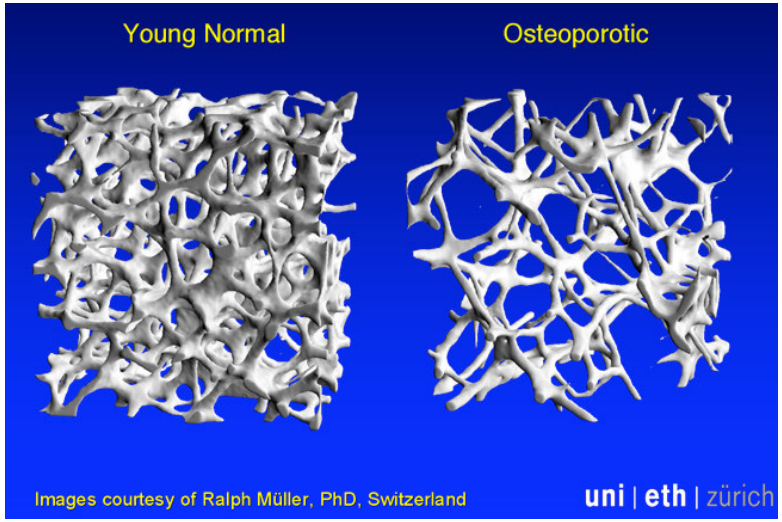


Adapted from Weinstein RS. *J Bone Miner Res* 15: 621, 2000

Cancer Treatment Induced Bone Loss (CTIBL)

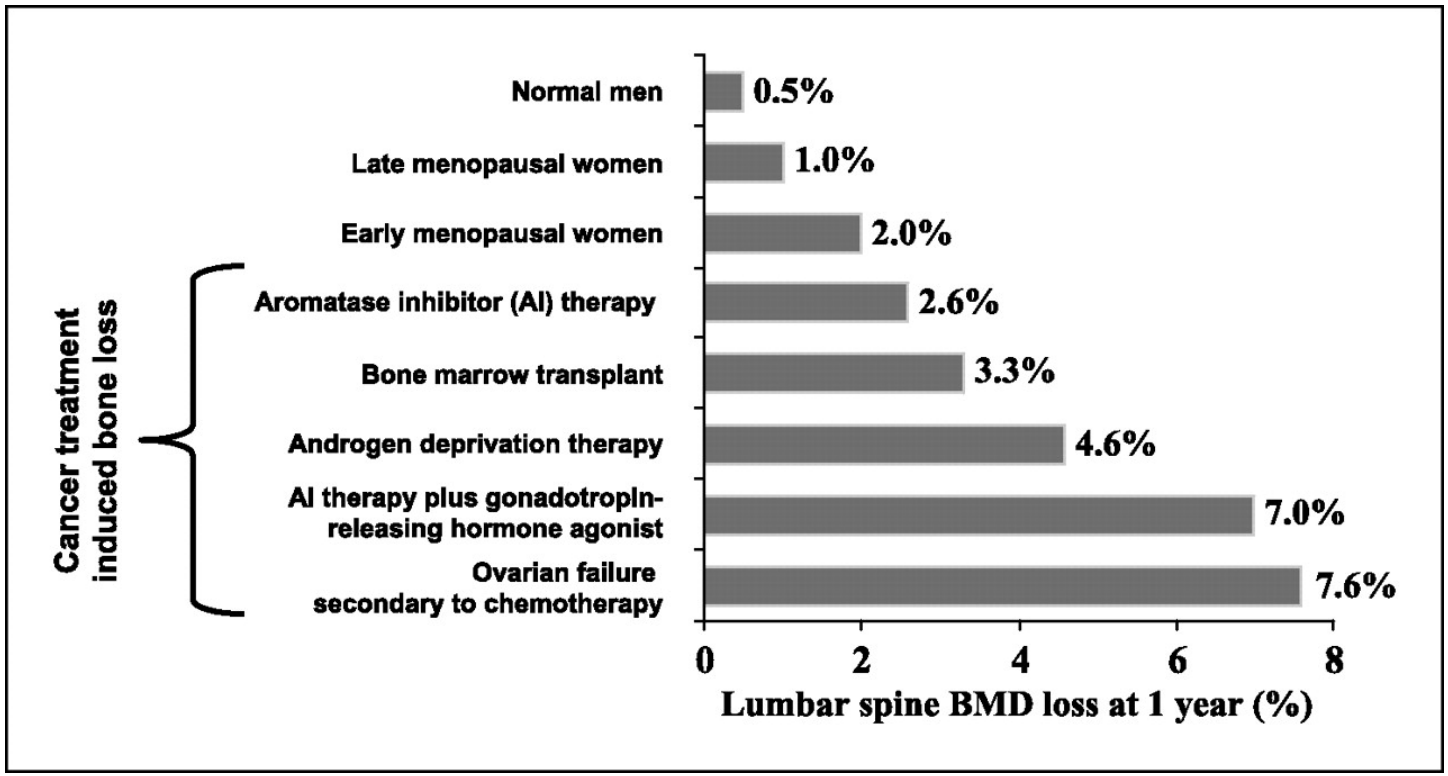
Rapid and severe bone loss resulting from cancer therapies that lead to estrogen (androgen) deprivation:

- Estrogen deprivation therapy
- Androgen deprivation therapy
- Chemotherapy
- Surgery (Castration)



Edwards BJ, et al. Osteoporos Int 2016

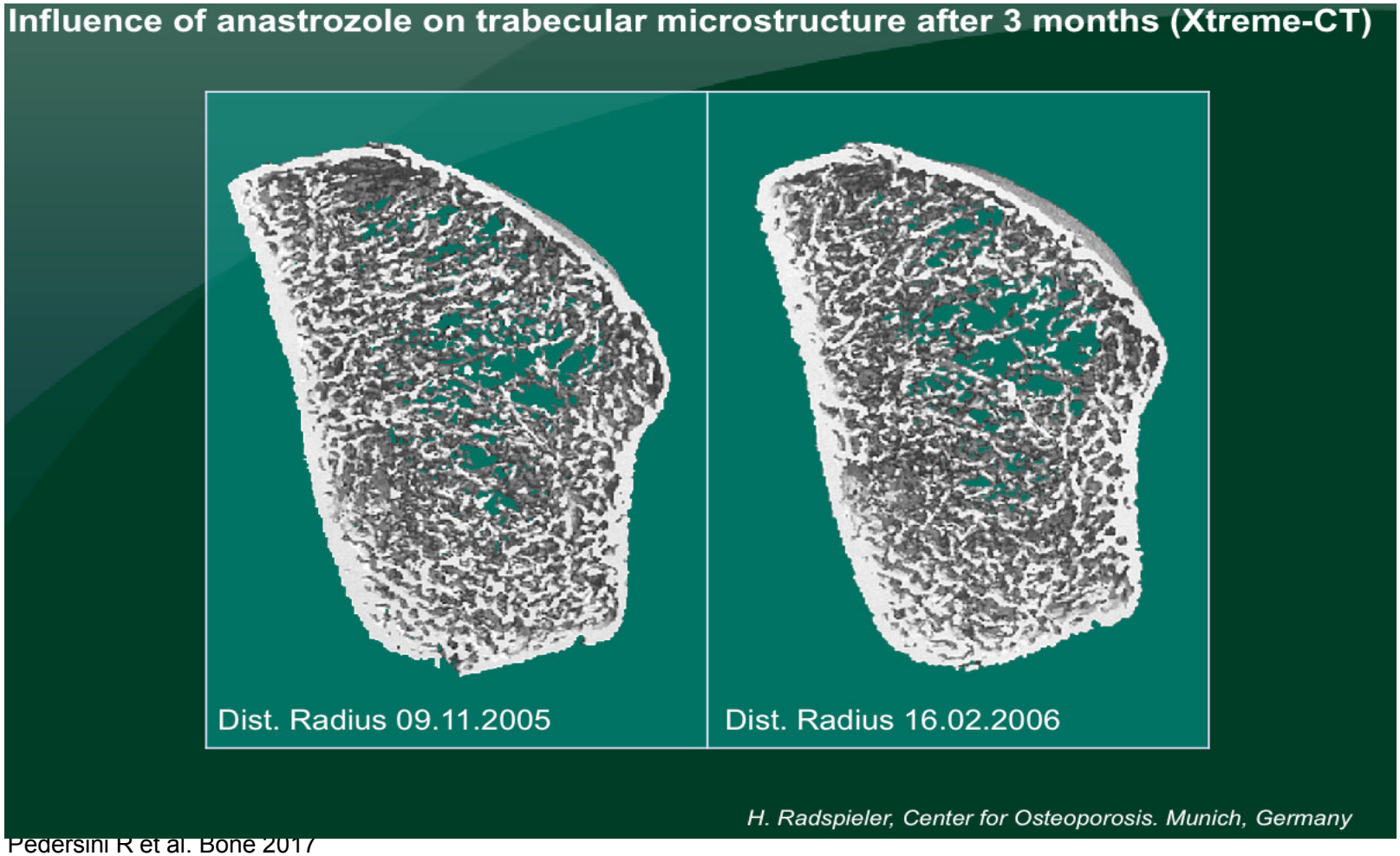
BONE LOSS AND CANCER THERAPY



Angela Hirbe et al. Clin Cancer Res 2006;12:6309s-6314s

Clinical Cancer Research
AACR American Association for Cancer Research

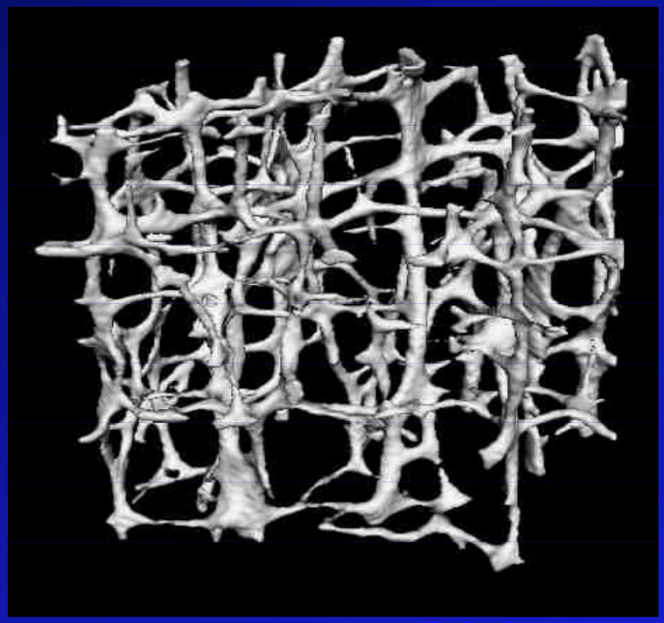
The CTIBL fracture risk is indipendent from BMD



Pedersini R et al. Bone 2017

Alterata “qualità” dell’osso

Geometria
Microarchitettura
Turnover
Proprietà del materiale
Accumulo di microdanni

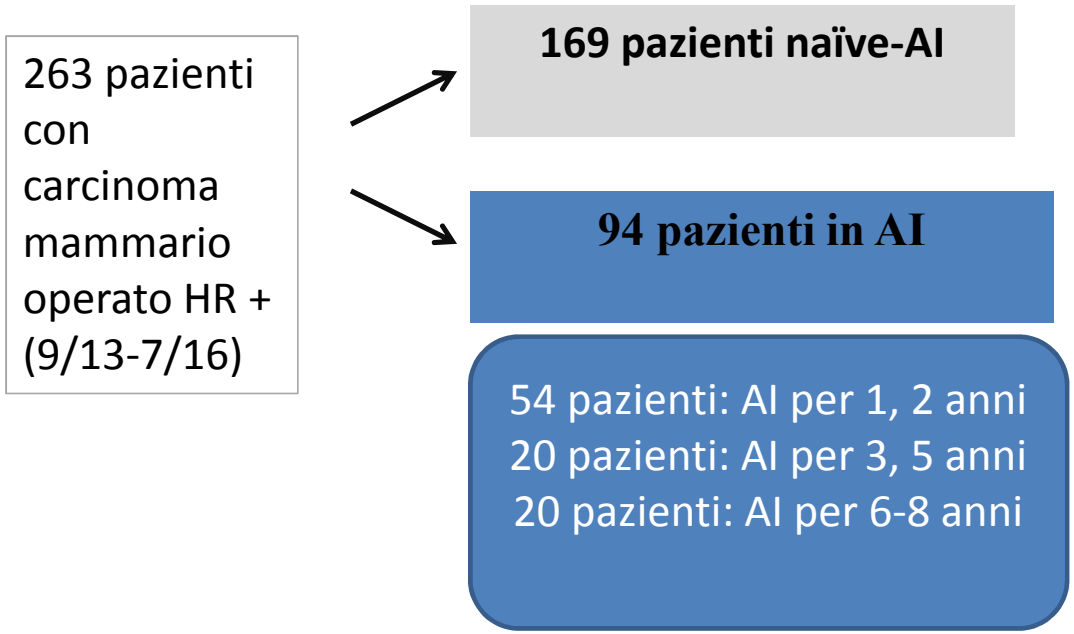


Full Length Article

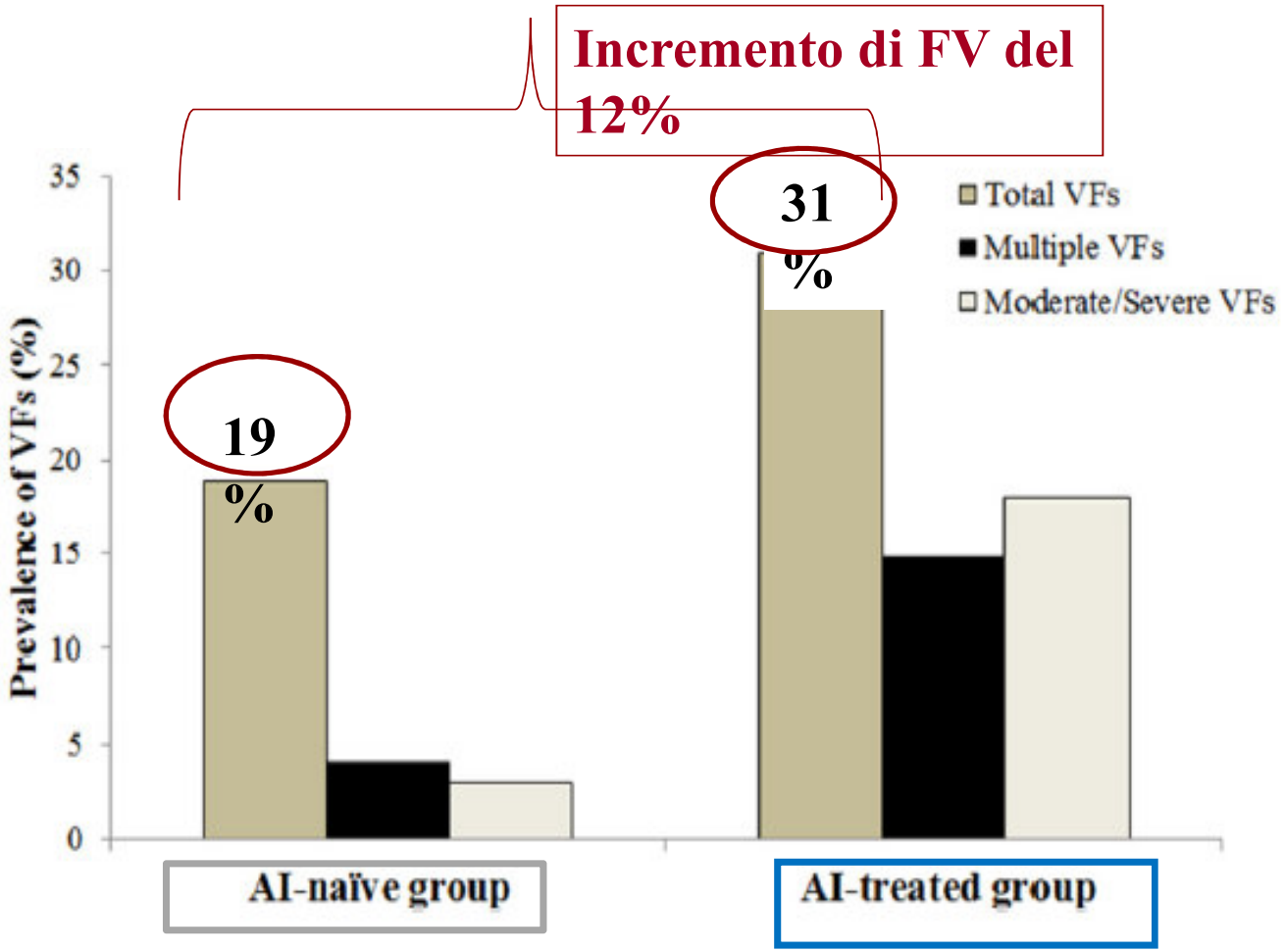
Morphometric vertebral fractures in breast cancer patients treated with adjuvant aromatase inhibitor therapy: A cross-sectional study

Bone 97 (2017) 147–152

Rebecca Pedersini [a,b], Sara Monteverdi [a,b], Gherardo Mazziotti [c], Vito Amoroso [a,*], Elisa Roca [a], Filippo Maffezzoni [d,e], Lucia Vassalli [a,b], Filippo Rodella [a,b], Anna Maria Formenti [d,e], Stefano Frara [f], Roberto Maroldi [e], Alfredo Berruti [a], Edda Simoncini [b], Andrea Giustina [f]



PREVALENZA E SEVERITA' DELLE FRATTURE VERTEBRALI



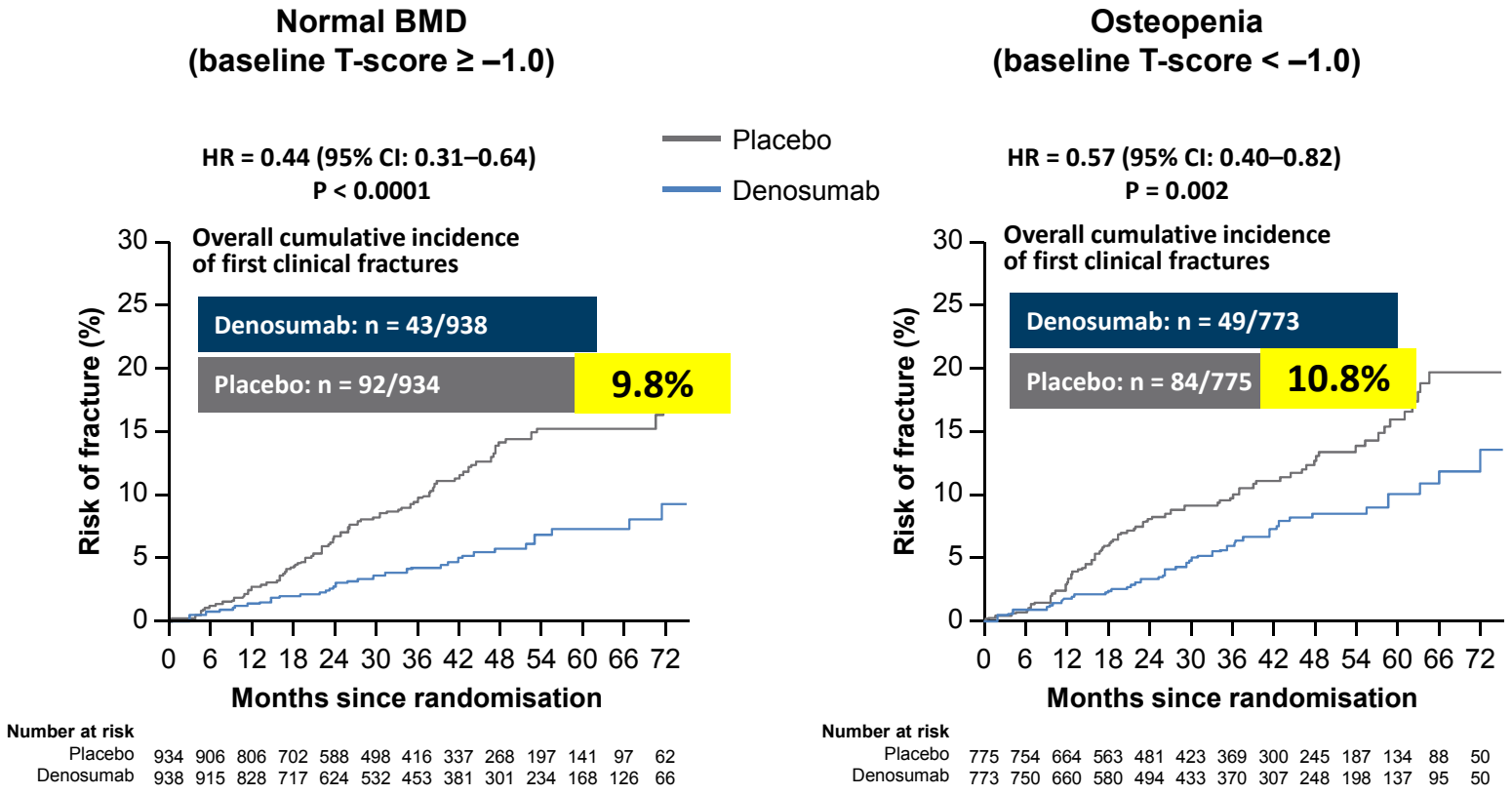
Pedersini R, Bone ; 97 (2017): 147-

FRATTURE VERTEBRALI PARAMETRI PREDITTIVI

	Groups	Patients without VFs	Patients with VFs	*p*-values
Age (years)	AI-naïve	64 (41–81)	68 (52–83)	**0.002**
	AI-treated	65 (51–85)*	66 (57–77)	0.52
BMI (kg/m^2)	AI-naïve	26 (18–39)	24 (18–34)	0.10
	AI-treated	25 (16–37)	27 (18–34)*	0.08
Prior chemotherapy (N, %)	AI-naïve	38 (27.7%)	8 (25.0%)	0.75
	AI-treated	19 (29.2%)	12 (41.4%)	0.25
Lumbar spine BMD (g/cm^2)	AI-naïve	0.874 (0.630–1.370)	0.858 (0.610–1.170)	0.37
	AI-treated	0.852 (0.571–1.070)*	0.824 (0.670–1.101)	0.75
Femoral neck BMD (g/cm^2)	AI-naïve	0.700 (0.540–1.072)	0.643 (0.470–1.020)	**0.04**
	AI-treated	0.679 (0.361–0.943)	0.707 (0.510–0.870)	0.19
Total hip BMD (g/cm^2)	AI-naïve	1.000 (0.580–1.930)	0.927 (0.772–1.194)	**0.007**
	AI-treated	0.949 (0.770–1.812)	0.955 (0.671–1.600)	0.82

Pedersini R, Bone ; 97 (2017): 147-152

ABCSG-18: il rischio di frattura nel gruppo placebo era sostanzialmente indipendete dalla BMD



Gnant M, et al. Lancet 2015;386:433–43.

NUTRITION RESEARCH 39 (2017) 1–13

Available online at www.sciencedirect.com

ScienceDirect

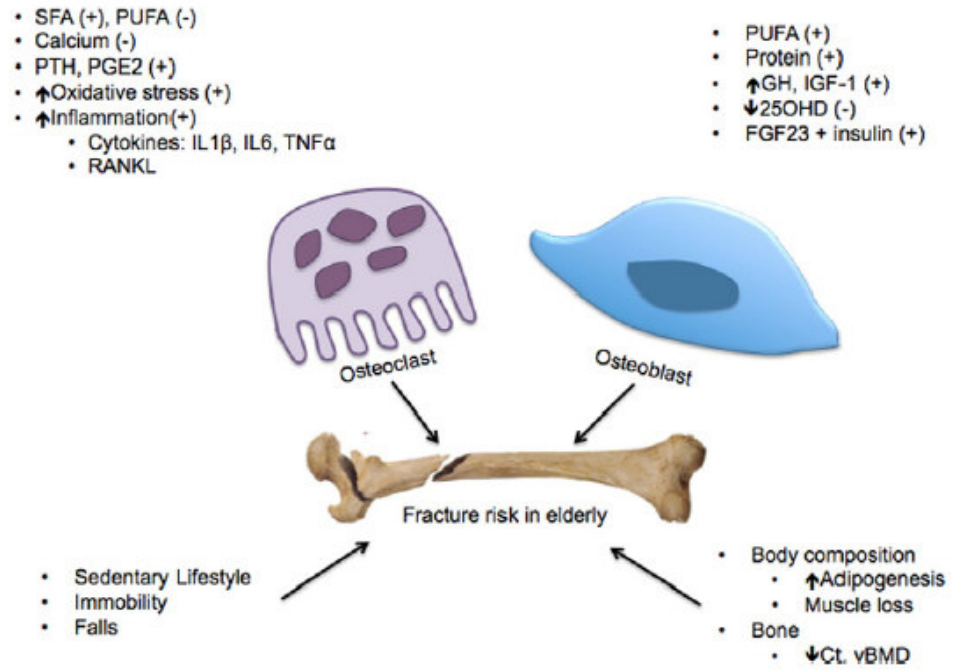
www.nrjournal.com

Review Article

Obesity is a concern for bone health with aging

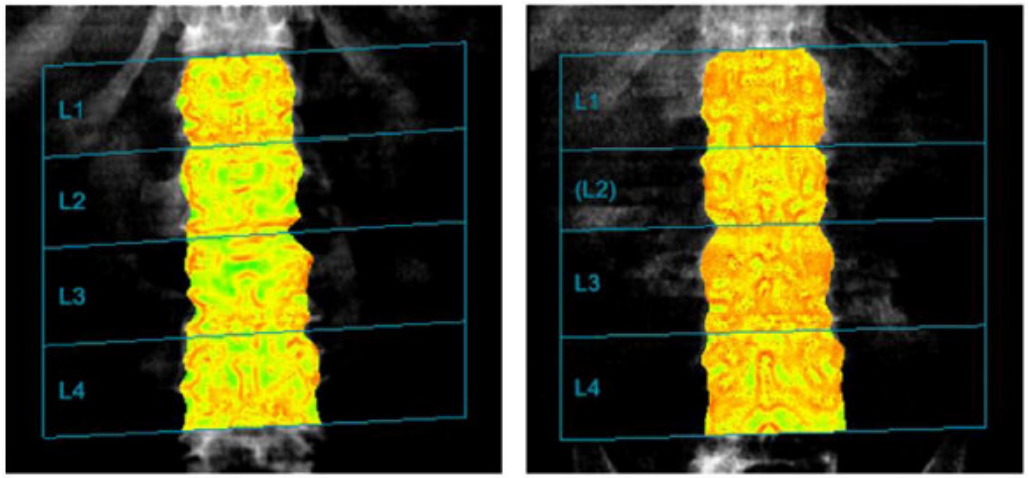
Sue A. Shapses, L. Claudia Pop, Yang Wang*

Department of Nutritional Sciences, Rutgers University, New Brunswick, NJ



Trabecular Bone Score (TBS)

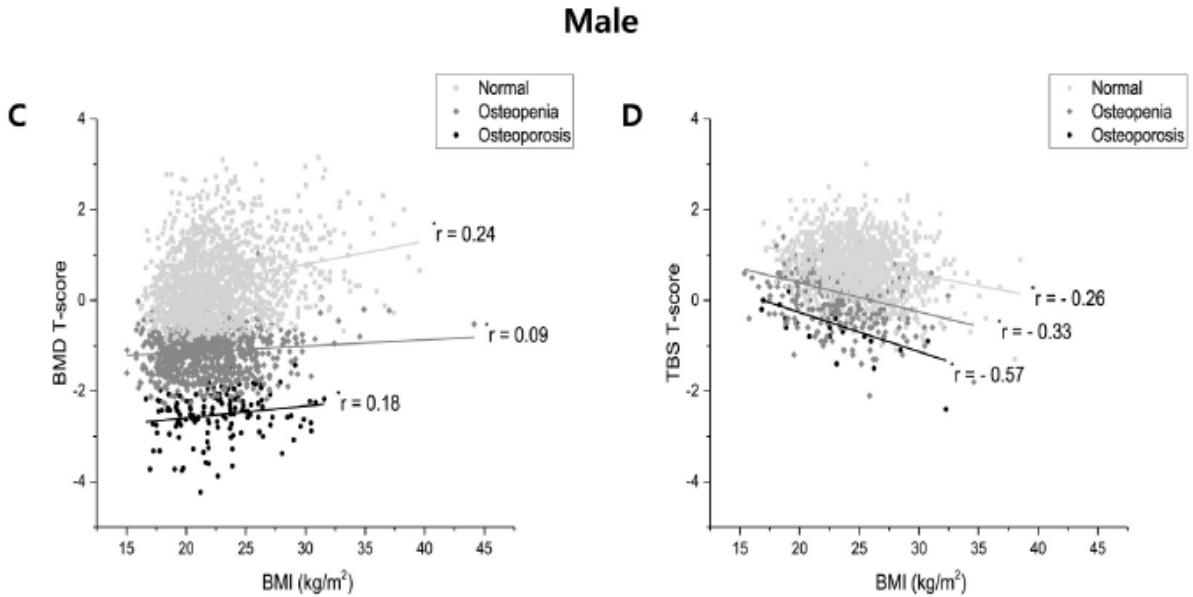
TBS is a texture parameter that quantifies the changes in pixel gray-level in DXA images



The correlation between bone mineral density/trabecular bone score and body mass index, height, and weight

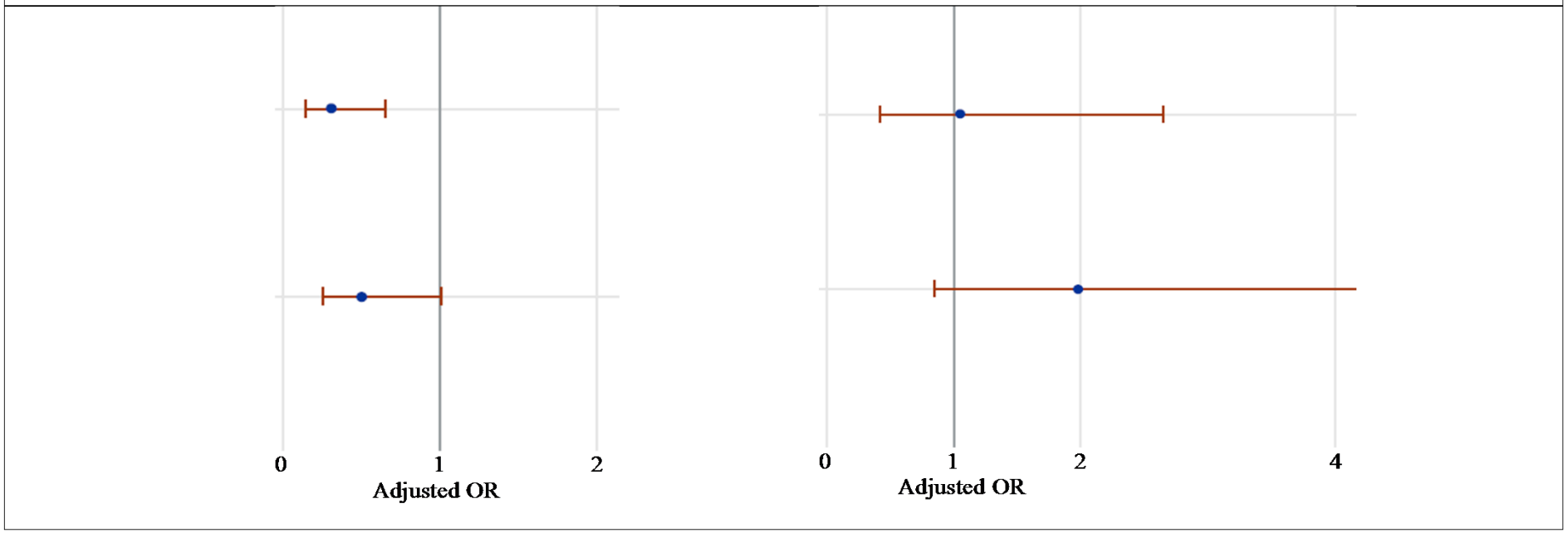
Young-Seong Kim [a], Jae-Joon Han [b], Jisu Lee [c], Han Seok Choi [d], Jin Hwan Kim [e], Taeyong Lee [c, *]

Osteoporosis and Sarcopenia 3 (2017) 98–103



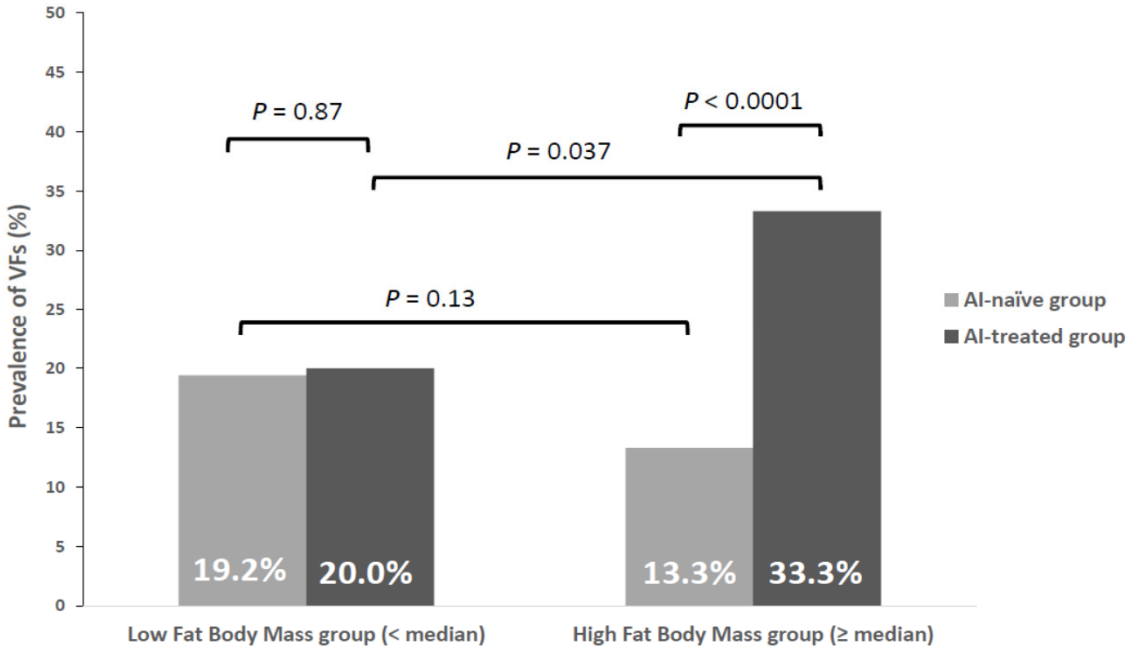
Interaction between Fat Body mass and fracture risk in AI naïve vs AI treated breast cancer patients

	AI-naïve patients			AI-treated patients			
Fat Body Mass Tertiles	**No. of events/No. of cases**	**Adjusted OR**	**95% CI**	**No. of events/No. of cases**	**Adjusted OR**	**95% CI**	**Exploratory *P* value for interaction**
2nd tertile vs. 1st tertile	**59/350**	**0.30**	**0.14-0-65**	**53/193**	**1.04**	**0.41-2.65**	**0.046**
3rd tertile vs. 1st tertile		**0.50**	**0.25-1.01**		**1.97**	**0.84-4.62**	**0.014**



Pedersini R et al, submitted for publication.

Vertebral Fracture Rates according to Fat Body Mass value



Pedersini R et al, submitted for publication.

Effetto differenziale dell'obesità fra uomo sano e in ADT

Soggetto sano obeso

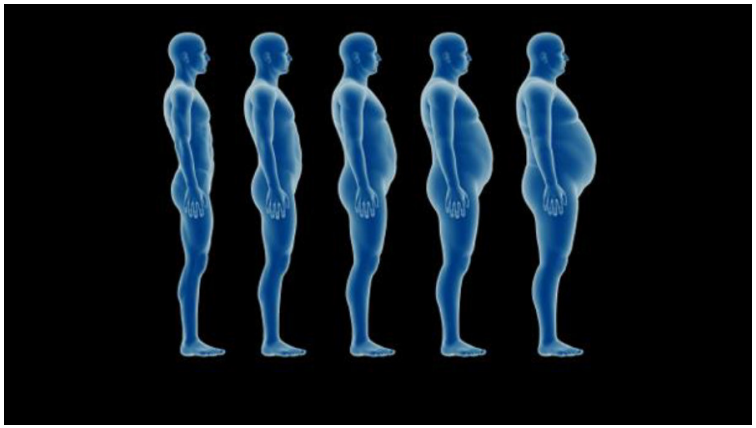
Effetto protettivo

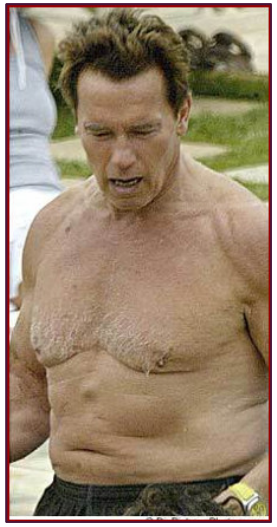
Soggetto obeso in androgeno deprivazione

Fragilità ossea aumentata

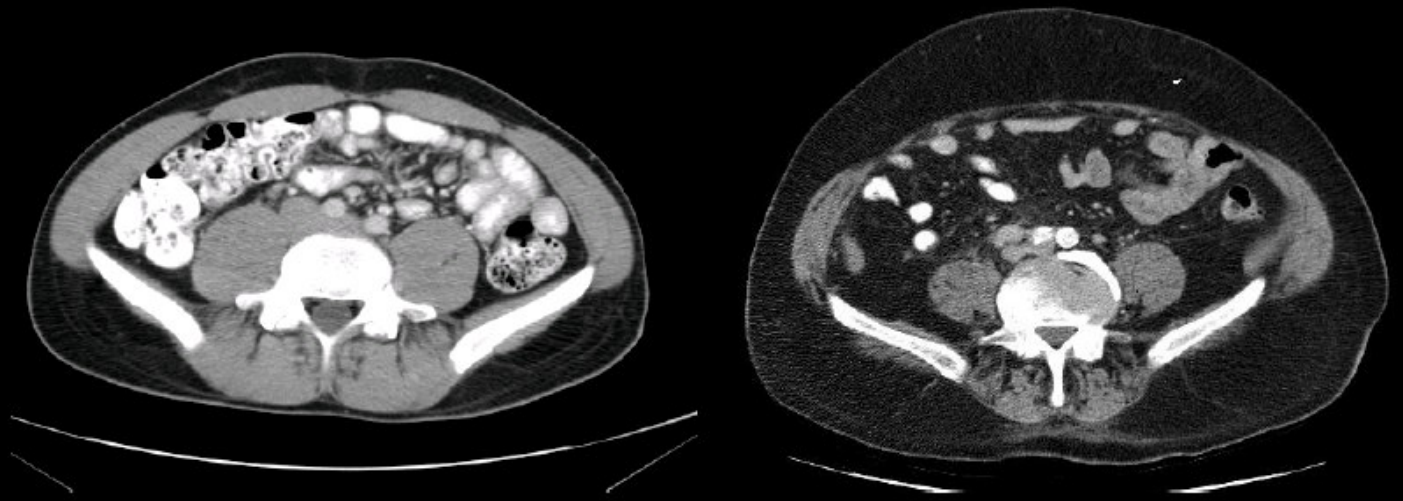
Interazione massa grassa e terapia ormonale possibile causa di alterazione della qualità dell’osso

ANDROGEN DEPRIVATION AND CHANGES IN BODY COMPOSITION





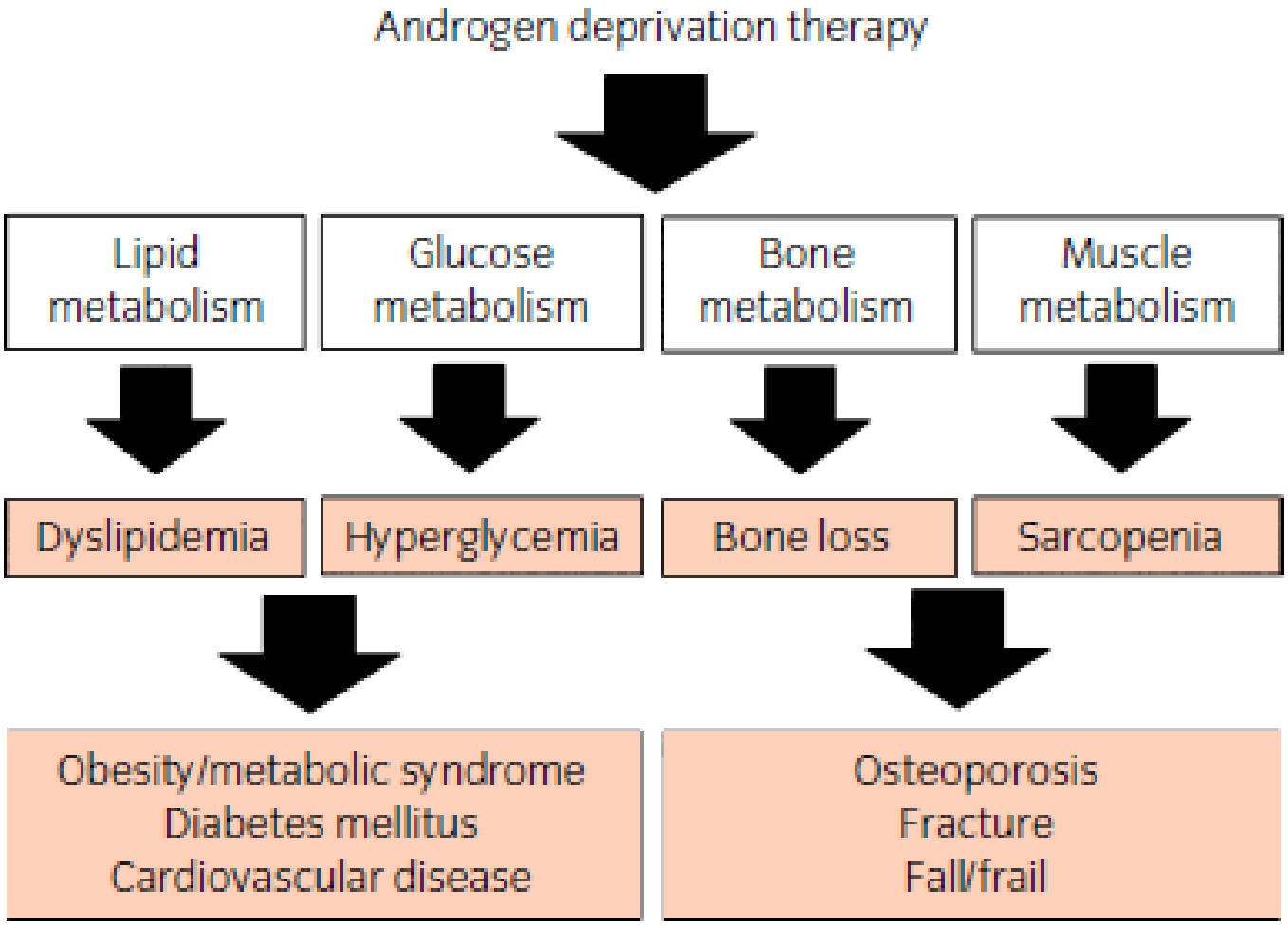
Abdominal Obesity and Sarcopenia during ADT



Eugonadal young man

Older man on ADT

Saylor PJ and Smith MR *et al* (2009) J Urol



Mitsuzuka K Int J Urol. 2018; 25(1):45-53

Endocrine (2015) 50:223–230
DOI 10.1007/s12020-015-0525-x

ORIGINAL ARTICLE

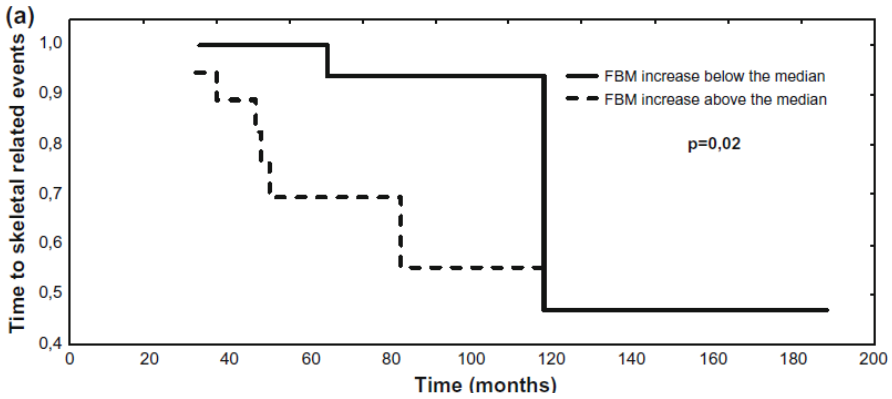
The fat body mass increase after adjuvant androgen deprivation therapy is predictive of prostate cancer outcome

Consuelo Buttigliero · Federica Vana · Valentina Bertaglia · Francesca Vignani · Cristian Fiori · Giangiacomo Osella · Francesco Porpiglia · Marcello Tucci · Giorgio Vittorio Scagliotti · Alfredo Berruti

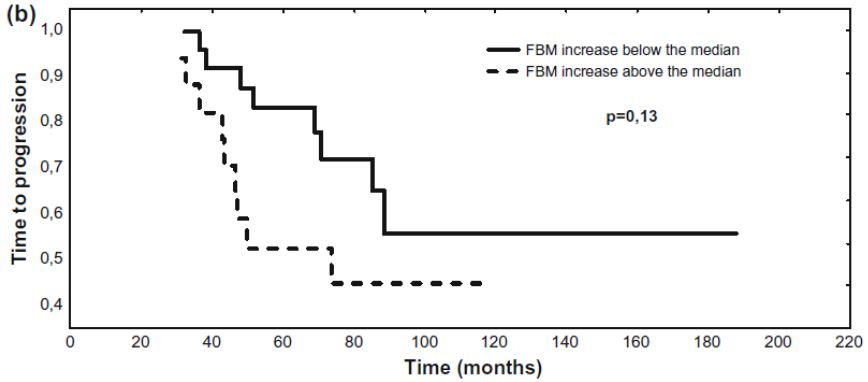
Table 2 Changes in bone mineral density, total fat body mass, and total lean body mass after androgen deprivation therapy

	Baseline	1 year	2 years	*p* value
Bone mineral density L2–L4 (g/cm^2)				
Mean (95 % CI)	0.943 (0.874–1.013)	0.933 (0.866–1.00)	0.927 (0.863–0.991)	$p < 0.03$
Fat body mass (g)				
Mean (95 % CI)	19,463 (17,143–21,783)	21,028 (18,964–23,093)	21,680 (19,427–23,932)	$p = 0.00$
Lean body mass (g)				
Mean (95 % CI)	50,216 (48,068–52,364)	49,553 (47,314–51,791)	49,377 (47,247–51,507)	$p < 0.03$

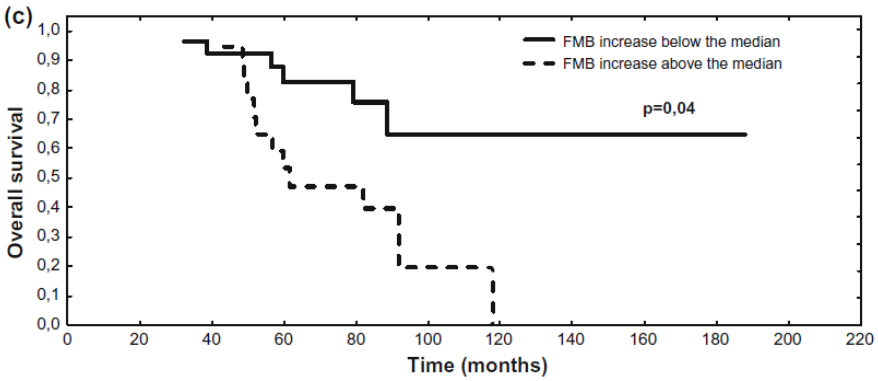
Time to first SRE



Progression Free Survival



Overall Survival



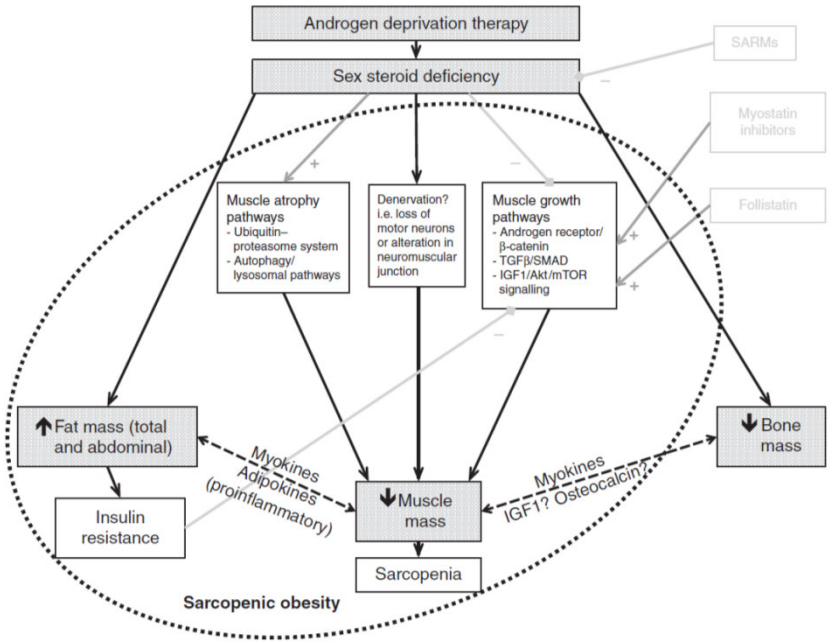
Buttigliero C et al Endocrine 2015

Muscle and bone effects of androgen deprivation therapy: current and emerging therapies

Ada S Cheung[1,2], Jeffrey D Zajac[1,2] and Mathis Grossmann[1,2]

[1]Department of Endocrinology, Austin Health, Heidelberg, Victoria, Australia
[2]Department of Medicine (Austin Health), The University of Melbourne, 300 Waterdale Road, Heidelberg West, Victoria 3081, Australia

Correspondence should be addressed to A S Cheung
Email
adac@unimelb.edu.au



La compromissione della salute dell'osso nel paziente con carcinoma prostatico sottoposto a ormonoterapia è conseguenza sia del danno osseo che delle modificazioni della composizione corporea indotti dai trattamenti.

LHRH-Agonists and Antagonists
KETOCONAZOLE
ABIRATERONE
ORTERONEL

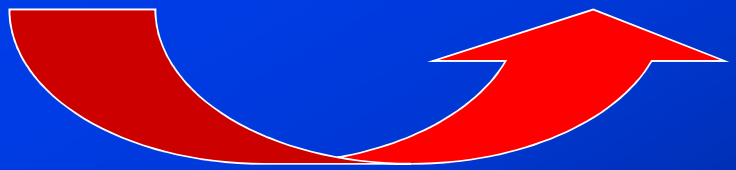
↓

ANDROGENS

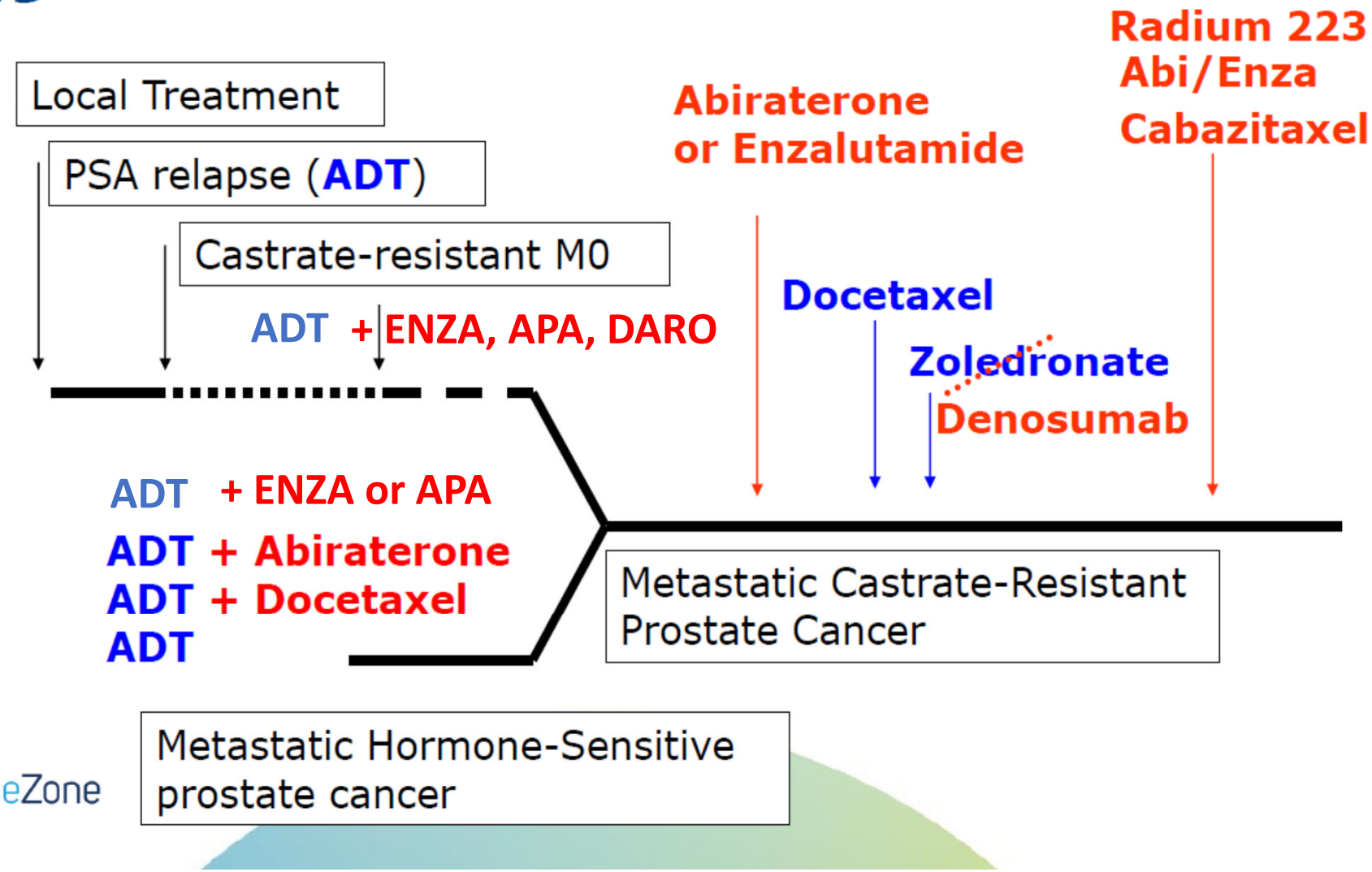
BICALUTAMIDE
~~CIPROTERONE~~
ENZALUTAMIDE
APALUTAMIDE
DAROLUTAMIDE

↓

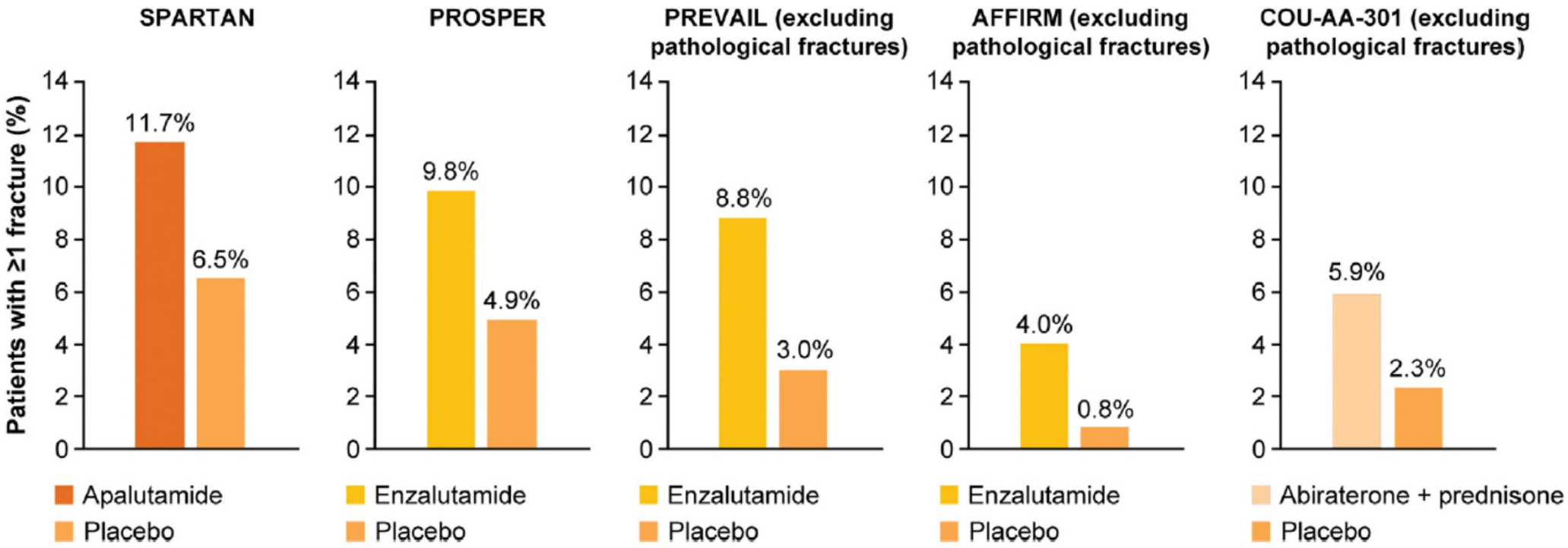
AR



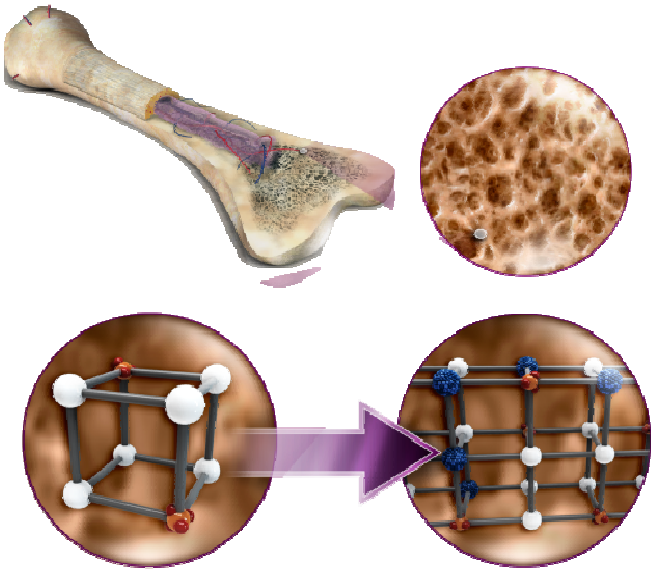
Systemic treatment for CRPC in 2019



TimeZone



O'Sullivan JM et al Eur Urol 2019

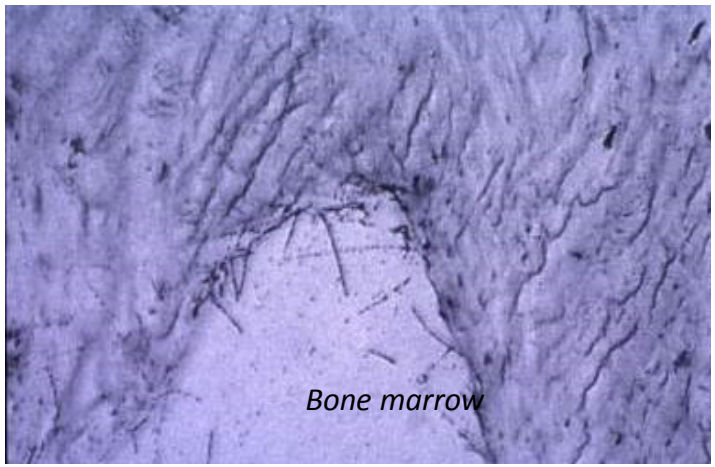


Hydroxyapatite, an inorganic mineral primarily consisting of calcium and phosphate ($Ca_{10}(PO_4)_6(OH)_2$), is the principal inorganic component of bone

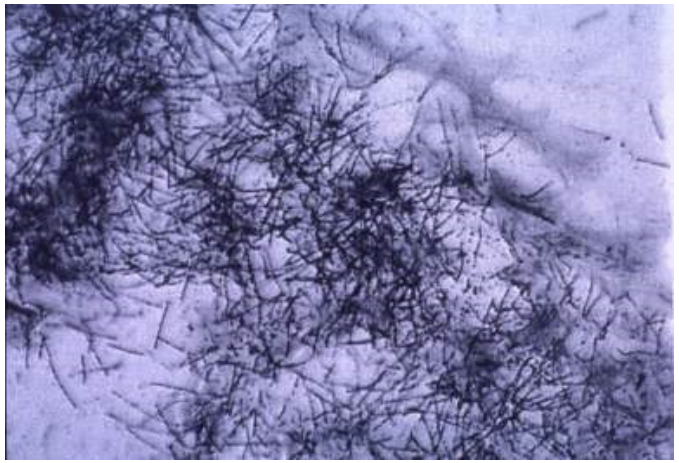
Radium-223 is incorporated like calcium into new hydroxyapatite deposits in the new bone, formed in and around bone metastases

Radium 223 has preferential uptake in areas of new bone formation

Normal spongious bone



Osteoblastic zone

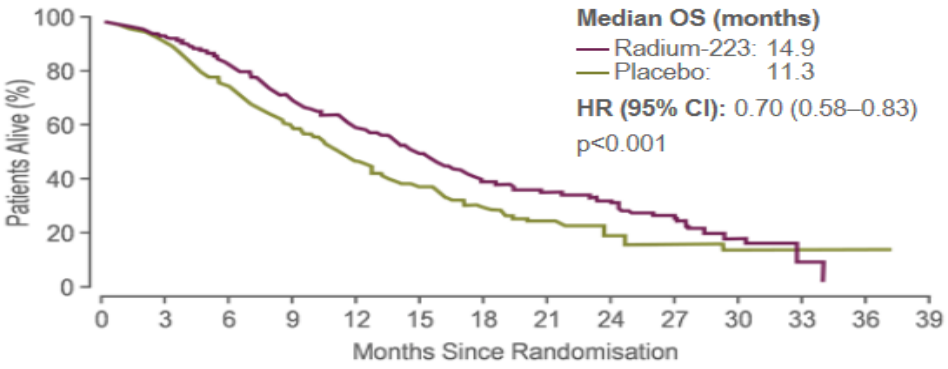


Microautoradiography from a dog injected with radium 223
Distribution of α-particle tracks in normal spongious bone and an osteoblastic zone

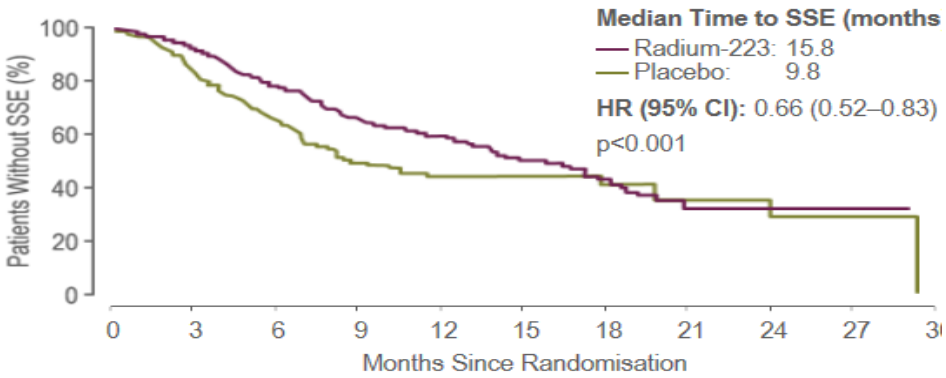
Bruland OS, et al. *Clin Cancer Res*. 2006;12:6250s-6257s.

ALSYMPCA: Phase 3 Study of Radium-223 vs Placebo in Men with mCRPC and Bone Metastases

Overall Survival

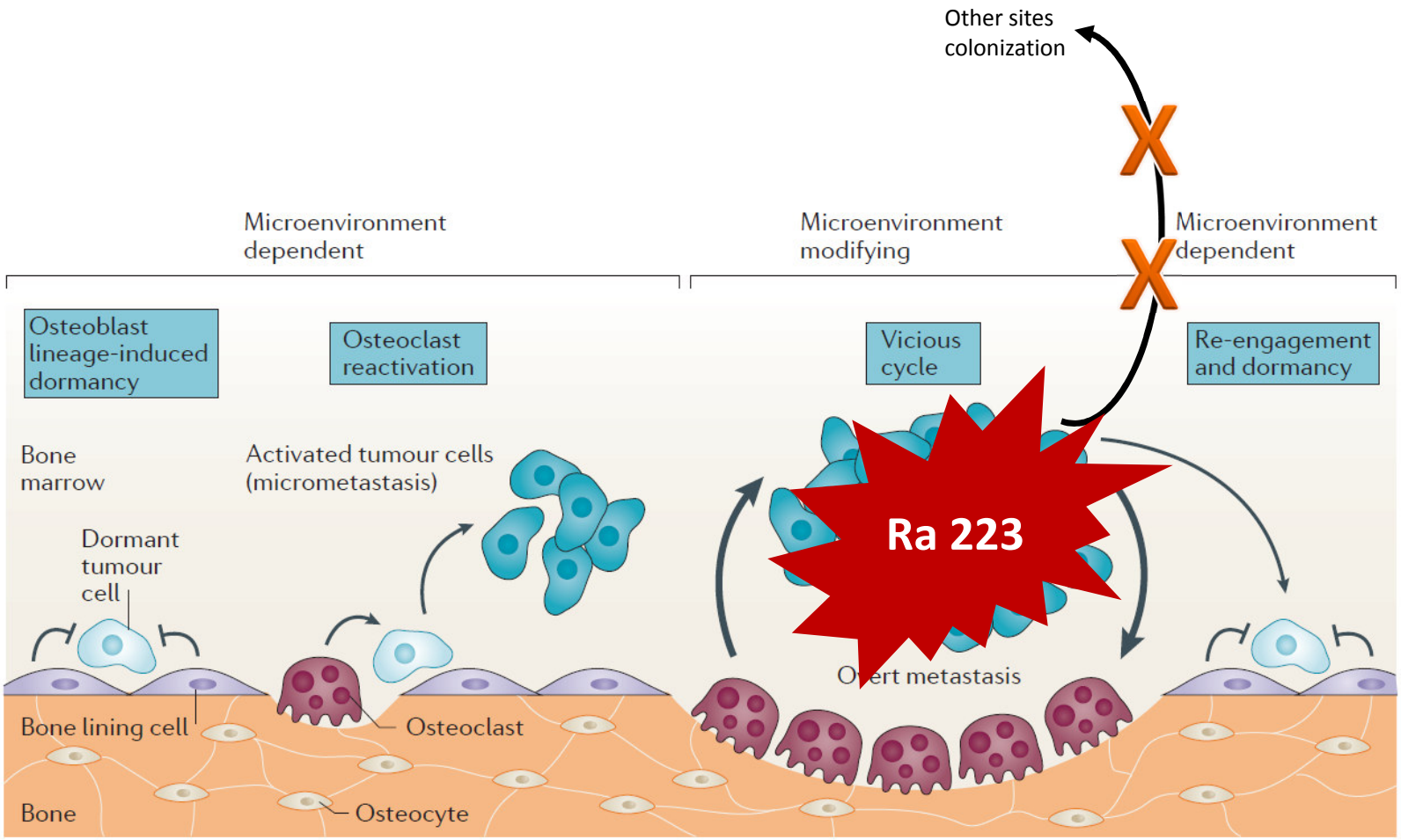


Time to Symptomatic Skeletal Event (SSE)



MUNICH 2018 ESMO congress

Parker C, et al. N Engl J Med. 2013;369:213–23.
mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; SSE, symptomatic skeletal event.



Modified from Croucher et al Nat Rev Cancer 2016, 16, 373

RADIUM RA 223 DICHLORIDE SIGNIFICANTLY REDUCED ALL RELEVANT BIOMARKERS VS PLACEBO

Median change from baseline to 4 weeks after last injection (week 16)

	Radium 223	Placebo	*P*
Bone ALP*	–66%	+9%	< 0.0001
Total ALP*	–46%	+31%	< 0.0001
PINP*	–63%	+38%	< 0.0001
CTX-I†	–31%	+32%	0.002
ICTP†	+15%	+43%	0.011
PSA‡	–24%	+45%	0.003

ALP, alkaline phosphatase; CTXI, cross-linked C-terminal telopeptides of type I collagen; ICTP, C-terminal telopeptides of type I collagen; PINP, amino-terminal procollagen propeptides of type.

*Bone formation marker.

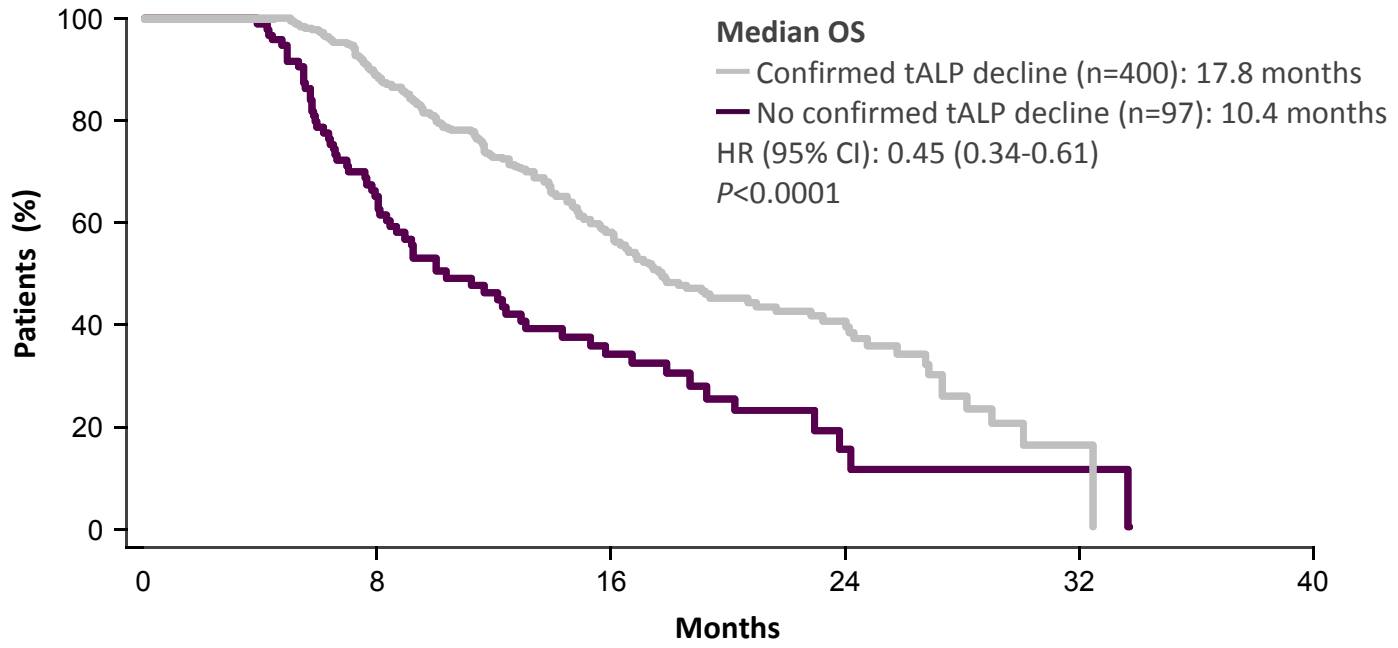
†Bone resorption marker.

‡Prostate tumor growth marker.

Nilsson S, et al. *Lancet Oncol* 2007;8:587-594.

Radium 223 Dichloride Patients With Confirmed tALP Decline at Week

Significantly Longer Overall Survival

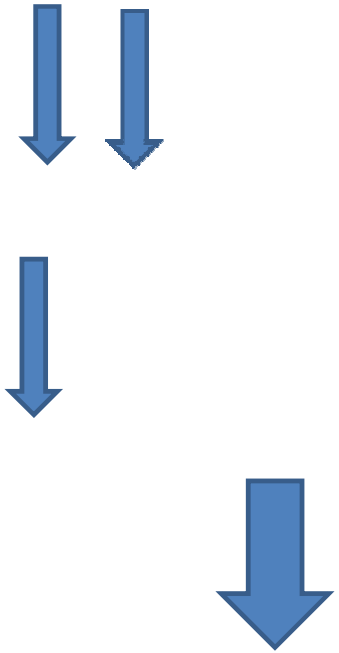


Median OS was significantly longer in radium-223 dichloride patients with confirmed tALP[a] decline at week 12 versus patients with no confirmed tALP decline (17.8 vs 10.4 months)

[a]Confirmed tALP decline was defined as *any* decrease from baseline at week 12, confirmed ≥3 weeks later.

Sartor O, et al. *J Clin Oncol.* 2013;31(suppl). Abstract 5080.

Radium 223 e metabolismo osseo



Riduzione attività osteoblastica

Riduzione attività osteoclastica

Basso turnover
Alterazione qualità
Aumento fragilità ossea

Evidenze a supporto di utilizzo in pratica clinica

- EAP Internazionale
- EAP –USA
- Studio Reassure – analisi ad interim
- Casistiche retrospettive internazionali (Flatiron, PARABO)

NON EVIDENZE DI INCREMENTO SSE DA UTILIZZO SEQUENZIALE IN PRATICA CLINICA

REVIEW

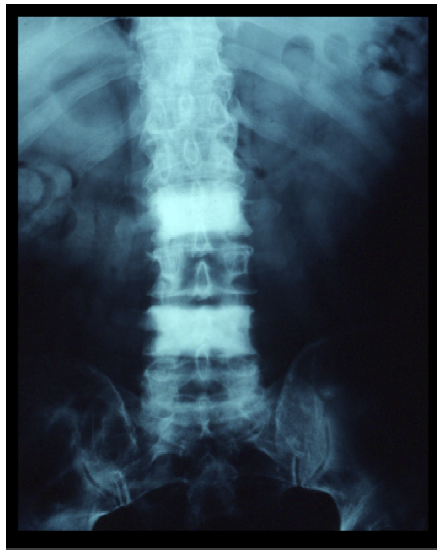
Novel Therapies for Metastatic Castrate-Resistant Prostate Cancer

Farshid Dayyani, Gary E. Gallick, Christopher J. Logothetis, Paul G. Corn

J Natl Cancer Inst 2011;103:1665–1675

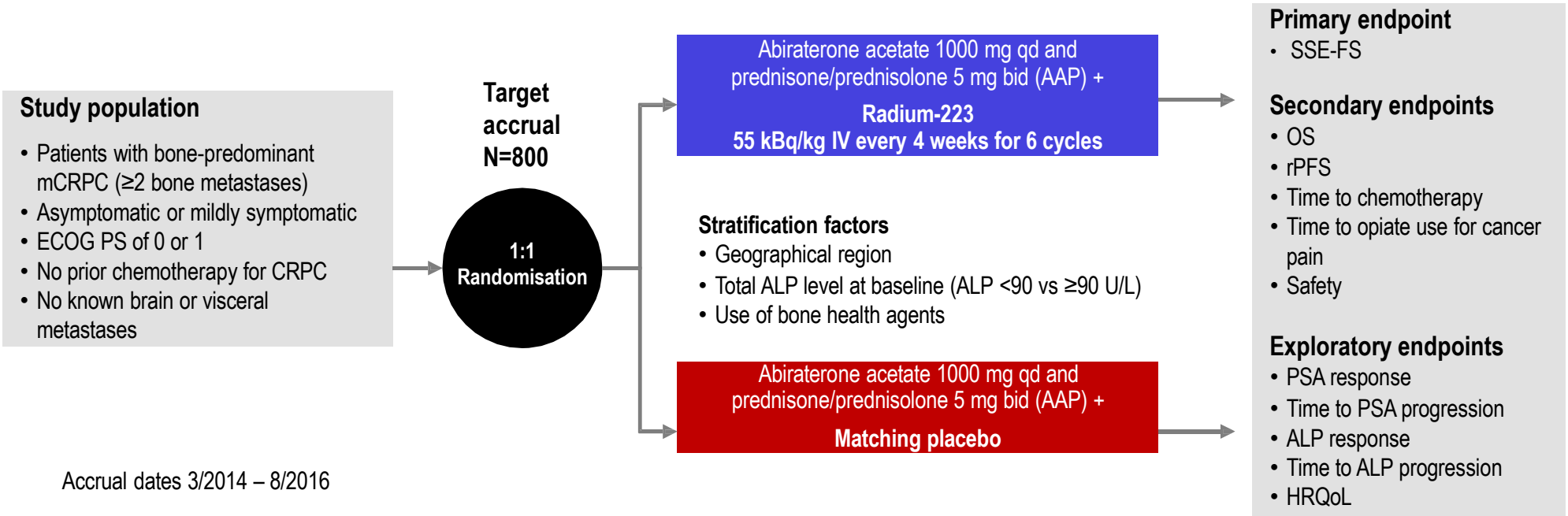
Targeting

Tumor cell ⇄ Tumor (bone) microenvironment



Radium 223

ERA 223 (NCT02043678)



Accrual dates 3/2014 – 8/2016

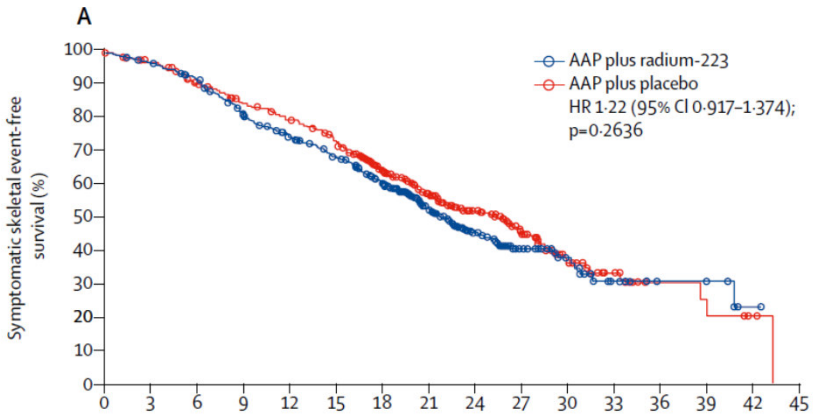
389 events were required to detect a 39% increase in SSE-FS using a test with a 2-sided alpha of 0.05, 90% power and 1:1 randomisation

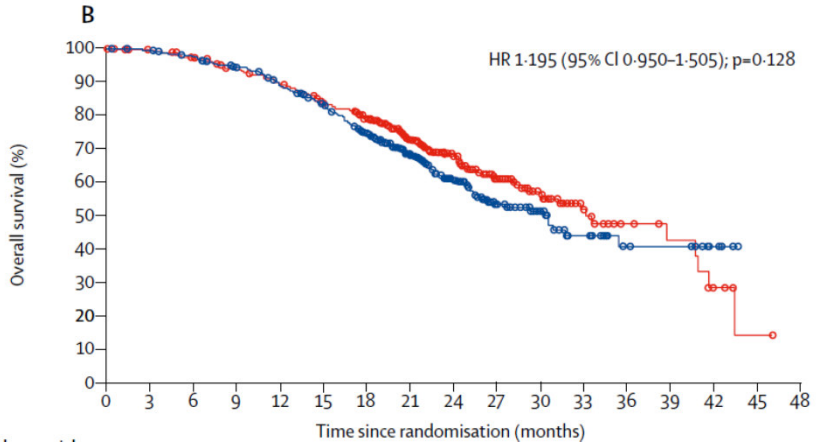
Bone health agents (denosumab or bisphosphonates) only permitted in patients receiving them at baseline; initiation during the study prohibited to prevent confounding effects.

ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiological progression-free survival; SSE-FS, symptomatic skeletal event-free survival.

Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial

Matthew Smith, Chris Parker, Fred Saad, Kurt Miller, Bertrand Tombal, Quan Sing Ng, Martin Boegemann, Vsevolod Matveev, Josep Maria Piulats, Luis Eduardo Zucca, Oleg Karyakin, Go Kimura, Nobuaki Matsubara, William Carlos Nahas, Franco Nolè, Eli Rosenbaum, Axel Heidenreich, Yoshiyuki Kakehi, Amily Zhang, Heiko Krissel, Michael Teufel, Junwu Shen, Volker Wagner, Celestia Higano

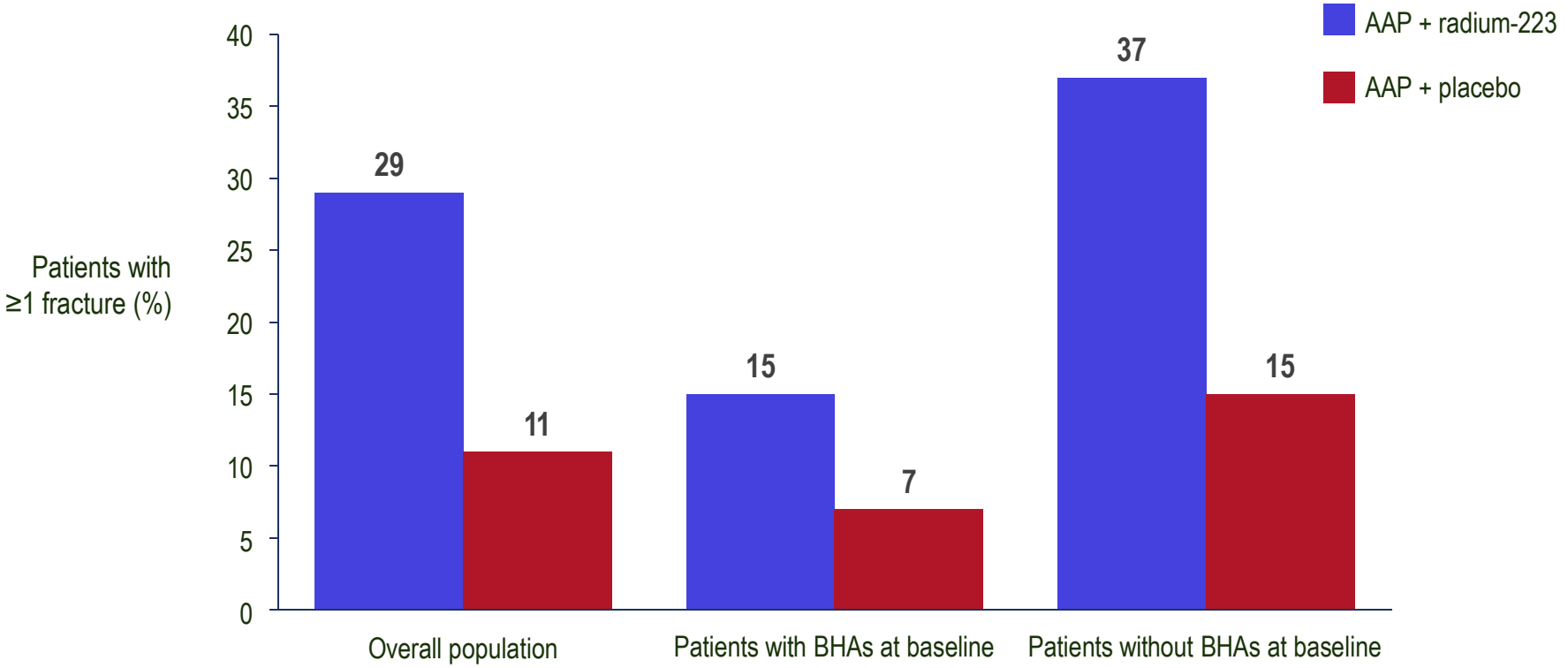




MUNICH 2018 ESMO congress

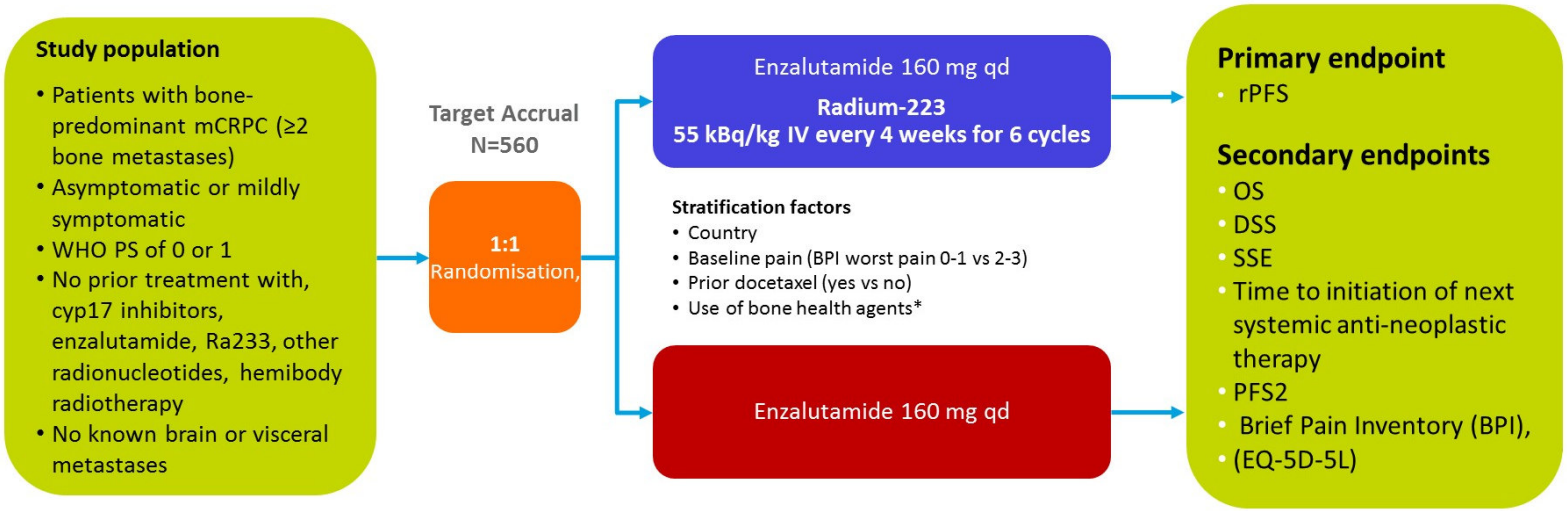
	AAP + radium-223	AAP + placebo
Patients with ≥1 SSE or death, n	196	190
Patients with death prior to SSE*, n (%)	74 (38)	73 (38)
Patients with SSE as first event		
EBRT, n (%)	73 (37)	80 (42)
Pathological fracture, n (%)	35 (18)	17 (9)
Spinal cord compression, n (%)	10 (5)	19 (10)
Orthopaedic surgical intervention, n (%)	4 (2)	1 (0.5)

Post-Hoc Subgroup Analysis of Fractures by Baseline BHA Use



AAP, abiraterone acetate and prednisone/prednisolone; BHA, bone health agent; NE, not estimable.

EORTC GUCG 1333 (PEACE III) original design



Bone health agents (denosumab or bisphosphonates) only permitted in patients receiving them at baseline; Initiation during study was prohibited to prevent confounding effects.

Timelines, impact of ERA 223 and role of IDMC

April 2017: Protocol version 3.0 - Amendment 4 –Adoption of PCWG3, allowable dose of prior docetaxel.

October 2017: IDMC review of the Safety look 1: no major safety concerns

14/03/2018: Urgent Safety Letter (14/03/2018): mandatory use of bone protecting agents and delayed initiation of Ra-223.

April 2018: IDMC review of the Safety look 2 incorporating results of ERA 223

- **Bone protecting agents (BPA), at the SSE preventing dose,** should be used in both arms of the trial for the duration of study treatment (including enzalutamide) or the maximum number of years allowed by local guidelines.
- For patients starting BPA just prior to randomization, a **minimum of 6 weeks** should exist between the start date of BPA and start date of Ra223. This delay does not apply to the start of enzalutamide.
- All skeletal events (fractures, spinal cord compression and surgery or radiation therapy to bone) that occurred after 14 March 2018 (urgent safety measure) should be promptly reported to pharmacovigilance.

Bone fractures and cumulative incidence safety population

Time point	Treatment and use of bone protecting agents			
	With exposure to BPA		Without exposure to BPA	
	Enza+Rad (N=39)	Enza (N=49)	Enza+Rad (N=37)	Enza (N=35)
	Cum Incidence (95% CI)*	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)
3 months	0 (-)	0 (-)	0 (-)	5.7 (1.0-16.7)
6 months	0 (-)	0 (-)	5.6 (1.0-16.3)	8.8 (2.2-21.0)
9 months	0 (-)	0 (-)	22.6 (10.6-37.3)	8.8 (2.2-21.0)
12 months	**0 (-)**	**0 (-)**	**37.4 (21.8-53.1)**	**12.4 (3.9-26.2)**
15 months	0 (-)	0 (-)	43.6 (26.8-59.3)	16.6 (5.9-32.0)
18 months	0 (-)	0 (-)	43.6 (26.8-59.3)	16.6 (5.9-32.0)

* the one fracture in this group occurred at month 27

Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial

Oliver Sartor, Robert Coleman, Sten Nilsson, Daniel Heinrich, Svein I Helle, Joe M O'Sullivan, Sophie D Fosså, Aleš Chodacki, Paweł Wiechno, John Logue, Anders Widmark, Dag Clement Johannessen, Peter Hoskin, Nicholas D James, Arne Solberg, Isabel Syndikus, Nicholas J Vogelzang, C Gillies O'Bryan-Tear, Minghua Shan, Øyvind S Bruland, Christopher Parker

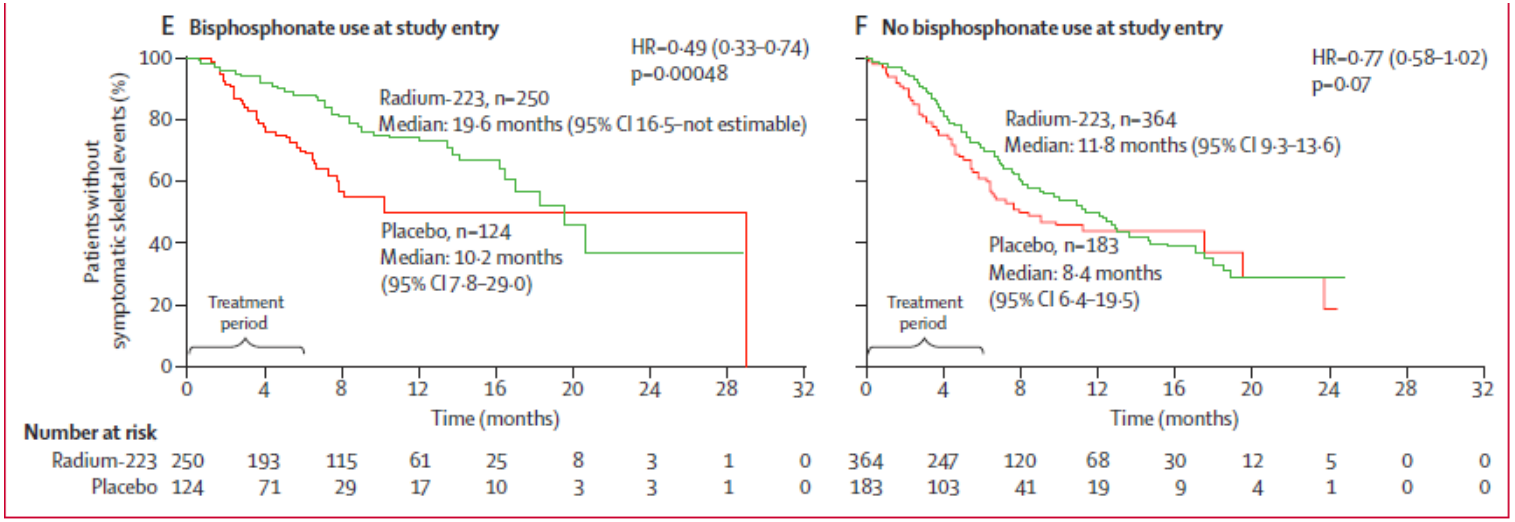


***Figure 2*: Kaplan–Meier estimates of time to first symptomatic skeletal event, by baseline stratification factors**
ALP=total alkaline phosphatase. HR=hazard ratio. SSE=symptomatic skeletal event. p values are for descriptive purpose only and not adjusted for multiplicity.

COME CAMBIA L'INDICAZIONE

Vecchia Indicazione	Nuova Indicazione (dal 13 luglio 2018)
Xofigo indicato per il trattamento di pazienti adulti con tumore della prostata resistente alla castrazione, con metastasi ossee sintomatiche e senza metastasi viscerali note.	Xofigo in monoterapia o in combinazione con analogo LHRH è indicato per il trattamento di pazienti adulti con tumore della prostata resistente alla castrazione metastatico (mCRPC), con metastasi ossee sintomatiche e senza metastasi viscerali note, in progressione dopo almeno due precedenti linee di terapia sistemica per mCRPC (oltre ad analogo LHRH), *o inelegibili per qualsiasi altro trattamento sistemico disponibile nel mCRPC*.

EMA/472321/2018 - 13 luglio 2018

Scheda Aifa: eleggibilità

Caratteristiche del paziente e aspetti rilevanti all'eleggibilità			
E	Estensione di malattia ossea (numero di lesioni scheletriche)	<6 metastasi	blocca
		6-20metastasi	
		>20 metastasi	
		Superscan	
E	Sintomatologia (*) (*misurato con la domanda 3 del Brief Pain Inventory - Short Form: punteggio variabile da 0 a 10 per la descrizione dell'episodio di dolore più intenso delle ultime 24 ore*)	Asintomatico (punteggio 0-1 secondo Brief Pain Inventory - Short Form)	blocca
		Lievemente sintomatico (punteggio 2-3 secondo Brief Pain Inventory - Short Form)	
		Francamente sintomatico (punteggio ≥4 secondo Brief Pain Inventory - Short Form)	

- Blocco per pazienti con meno di 6 sedi ossee di malattia
- Blocco per pazienti asintomatici (BPI-SF 0-1)

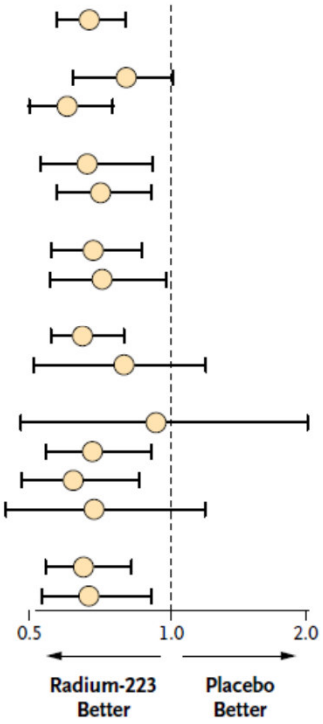
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

Subgroup	Radium-223	Placebo	Radium-223	Placebo	Hazard Ratio (95% CI)
	no. of patients		*median overall survival (mo)*		
All patients	614	307	14.9	11.3	0.70 (0.58–0.83)
Total ALP level at baseline					
<220 U/liter	348	169	17.0	15.8	0.82 (0.64–1.07)
≥220 U/liter	266	138	11.4	8.1	0.62 (0.49–0.79)
Current bisphosphonate use					
Yes	250	124	15.3	11.5	0.70 (0.52–0.93)
No	364	183	14.5	11.0	0.74 (0.59–0.92)
Previous docetaxel use					
Yes	352	174	14.4	11.3	0.71 (0.56–0.89)
No	262	133	16.1	11.5	0.74 (0.56–0.99)
Baseline ECOG performance-status score					
0 or 1	536	265	15.4	11.9	0.68 (0.56–0.82)
≥2	77	41	10.0	8.4	0.82 (0.50–1.35)
Extent of disease					
<6 metastases	100	38	27.0	NE	0.95 (0.46–1.95)
6–20 metastases	262	147	13.7	11.6	0.71 (0.54–0.92)
>20 metastases	195	91	12.5	9.1	0.64 (0.47–0.88)
Superscan	54	30	11.3	7.1	0.71 (0.40–1.27)
Opioid use					
Yes	345	168	13.9	10.4	0.68 (0.54–0.86)
No	269	139	16.4	12.8	0.70 (0.52–0.93)



I sintomi

Scheda AIFA: paziente candidabile a Ra223 per BPI-SF ≥ 2

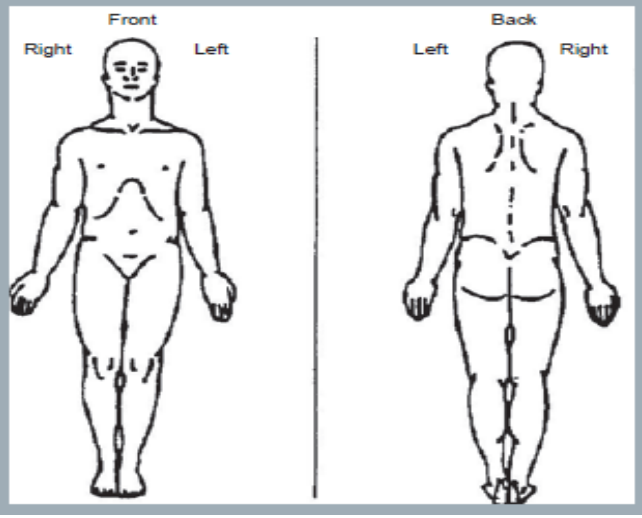
STUDY ID #: _____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Brief Pain Inventory (Short Form)

Date: ____/____/____ **Time:** _____

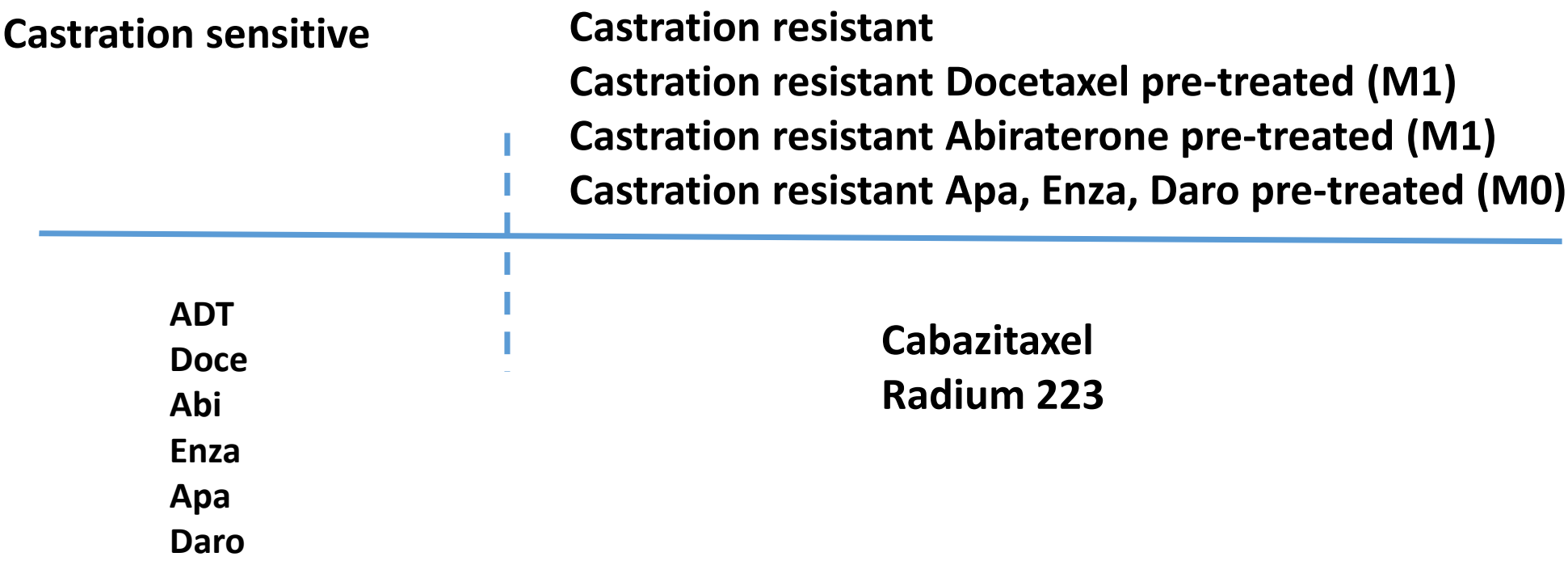
Name: _____ _____ _____
Last First Middle Initial

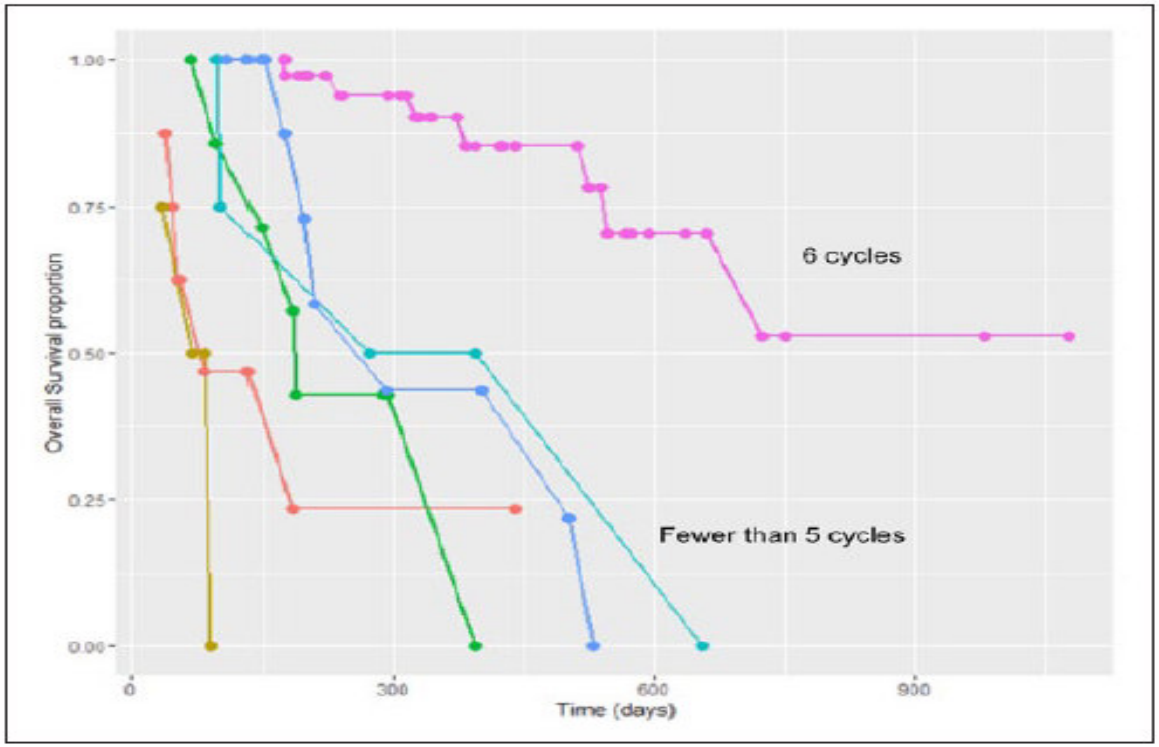
1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?
   1. Yes 2. No
2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.
   0 1 2 3 4 5 6 7 8 9 10
   No Pain — Pain as bad as you can imagine
4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.
   0 1 2 3 4 5 6 7 8 9 10
   No Pain — Pain as bad as you can imagine
5. Please rate your pain by circling the one number that best describes your pain on the average.
   0 1 2 3 4 5 6 7 8 9 10
   No Pain — Pain as bad as you can imagine
6. Please rate your pain by circling the one number that tells how much pain you have right now
   0 1 2 3 4 5 6 7 8 9 10
   No Pain — Pain as bad as you can imagine

Prostate cancer M1 : 2020



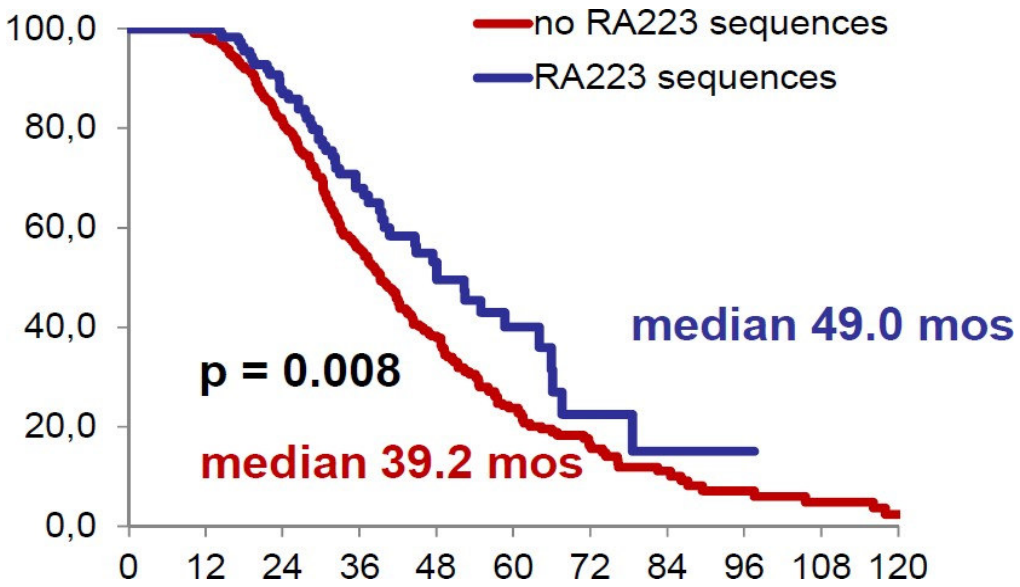


Il numero di cicli ricevuti si associa alla sopravvivenza globale e alla sopravvivenza libera da progressione.

Per massimizzare l'efficacia della terapia, bisogna selezionare correttamente il paziente in modo che abbia l'opportunità di completare tutti i cicli previsti.

Boni et al, Tumori J 2018

Sequencing Ra223 for mCRPC patients in the daily practice: preliminary results from a retrospective study in Italian Centers



In pts treated with 3 or 4 ADs that included Ra223, the median OS was significantly longer compared to that of pts whose treatment sequence did not include RA223

Caffo et al ASCO GU2018 – San Francisco poster # 32

OVER 3000 XOFIGO PATIENTS OBSERVED IN A REAL-WORLD SETTING

FLATIRON[2] (N=625)

STUDY DESIGN: Retrospective study of Xofigo in patients with prior abiraterone or enzalutamide use from the Flatiron Health electronic health records database, a longitudinal, demographically and geographically diverse database

PATIENT POPULATION: 187 (30%) and 164 (26%) patients received prior abiraterone or enzalutamide, respectively

Median follow-up: 7 months, prior abiraterone and prior enzalutamide groups; 9 months, overall cohort

PARABO[3] (N=333)

STUDY DESIGN: Ongoing, prospective, single-arm observational study of mCRPC patients with bone metastases who received Xofigo in clinical practice in Germany

PATIENT POPULATION: 70 (21%) patients had completed prior abiraterone treatment

Median follow-up: 7.9 months, overall cohort

REASSURE[4] (N=1435)

STUDY DESIGN: A prospective, non-interventional interim review of patients treated with Xofigo from North America, South America, and Europe, with a 7-year follow-up

PATIENT POPULATION: 431 (30%) patients received prior abiraterone (220 with BHAs, 211 without BHAs) and 675 (47%) were abiraterone-naive (302 with BHAs, 373 without BHAs)

Median follow-up: 9.1 months, overall cohort

iEAP[5] (N=708)

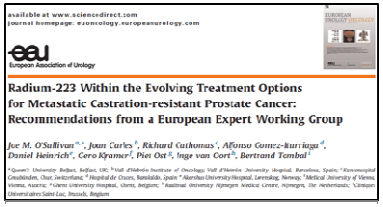
STUDY DESIGN: Open-label, single-arm international trial of Xofigo in patients with ≥2 bone metastases

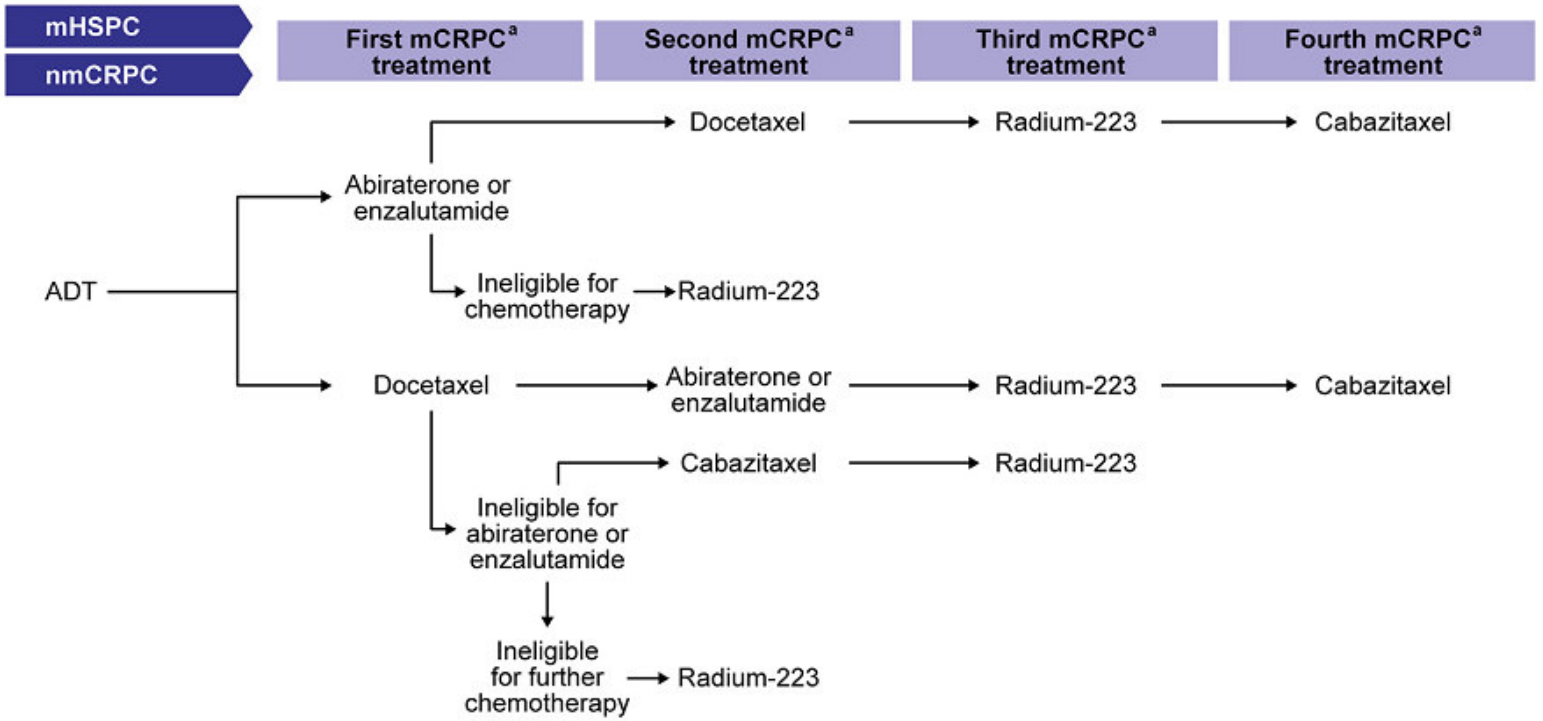
PATIENT POPULATION: 223 (31%) patients received prior abiraterone and 321 (45%) were abiraterone-naive

- Patients who received prior anticancer therapies were included; use of BHAs was permitted during Xofigo treatment

Median follow-up not reported.

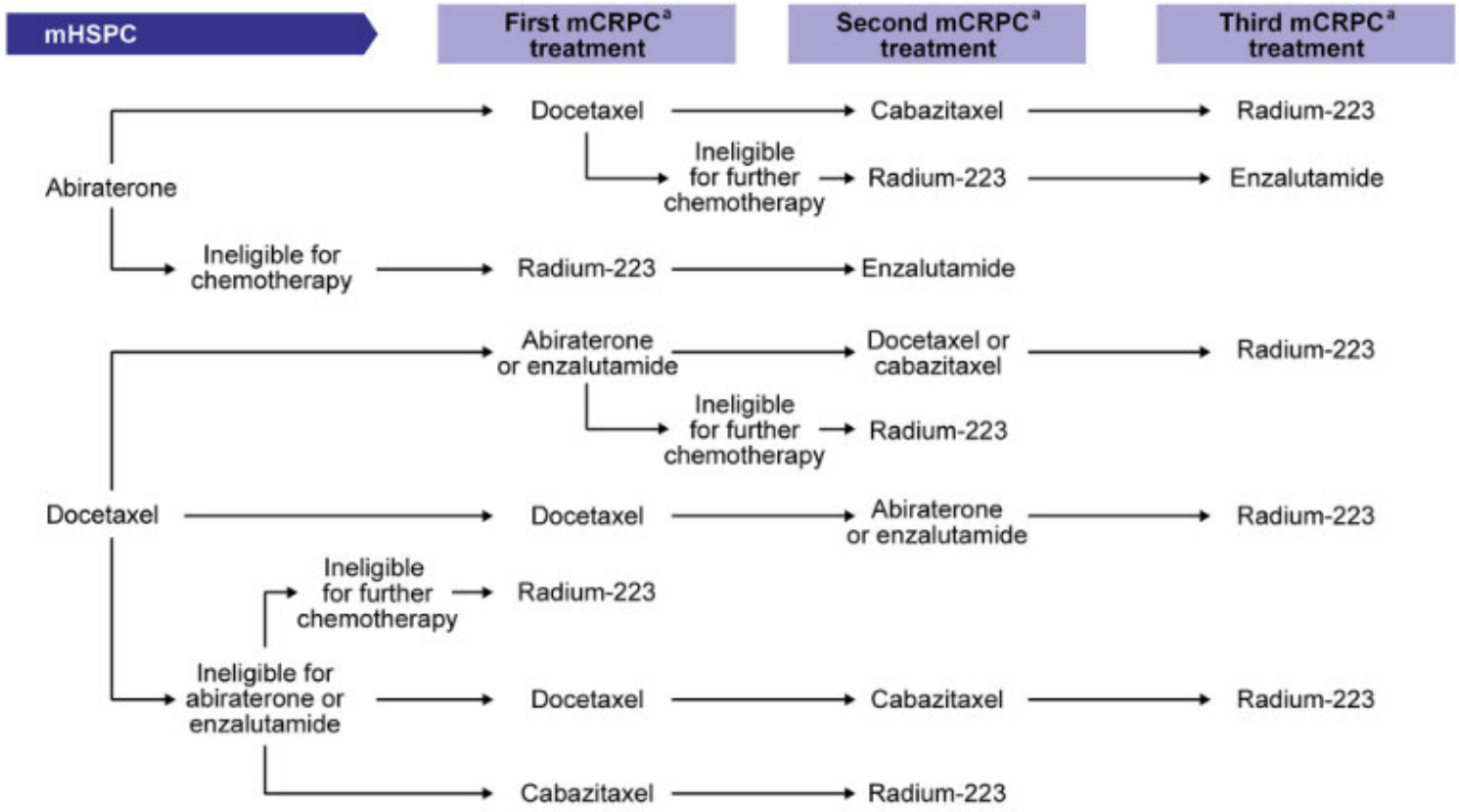
ADT in HSPC





O'Sullivan et al Eur Urol Apr 2019

Abiraterone o docetaxel in HPSC



O'Sullivan et al Eur Urol Apr 2019

Conclusioni

Radium 223 è un farmaco efficace nel trattamento del mCRPC

L’impiego delle moderne (e più efficaci) terapie nel paziente con carcinoma prostatico
ha eidenziato l’importanza delle misure preventive del rischio fratturativo

L’utilizzo di bisfosonati in associazione a Radium 223 non è controindicato e va impiegato
In tutti i casi in cui si ritenga il paziente ad alto rischio di fratture: **attenzione all’uso concomitante di steroidi**