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Il Radio-223 Dicloruro nel Trattamento del Carcinoma metastatico della Prostata

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Prostate cancer: incidence

Estimated New Cases

Males

Prostate	180,890	21%
Lung & bronchus	117,920	14%
Colon & rectum	70,820	8%
Urinary bladder	58,950	7%
Melanoma of the skin	46,870	6%
Non-Hodgkin lymphoma	40,170	5%
Kidney & renal pelvis	39,650	5%
Oral cavity & pharynx	34,780	4%
Leukemia	34,090	4%
Liver & intrahepatic bile duct	28,410	3%
All Sites	**841,390**	**100%**

Siegel R et al. Cancer Statistics 2016
Cancer J Clin 2016;66:7-30

Prostate cancer: death rate

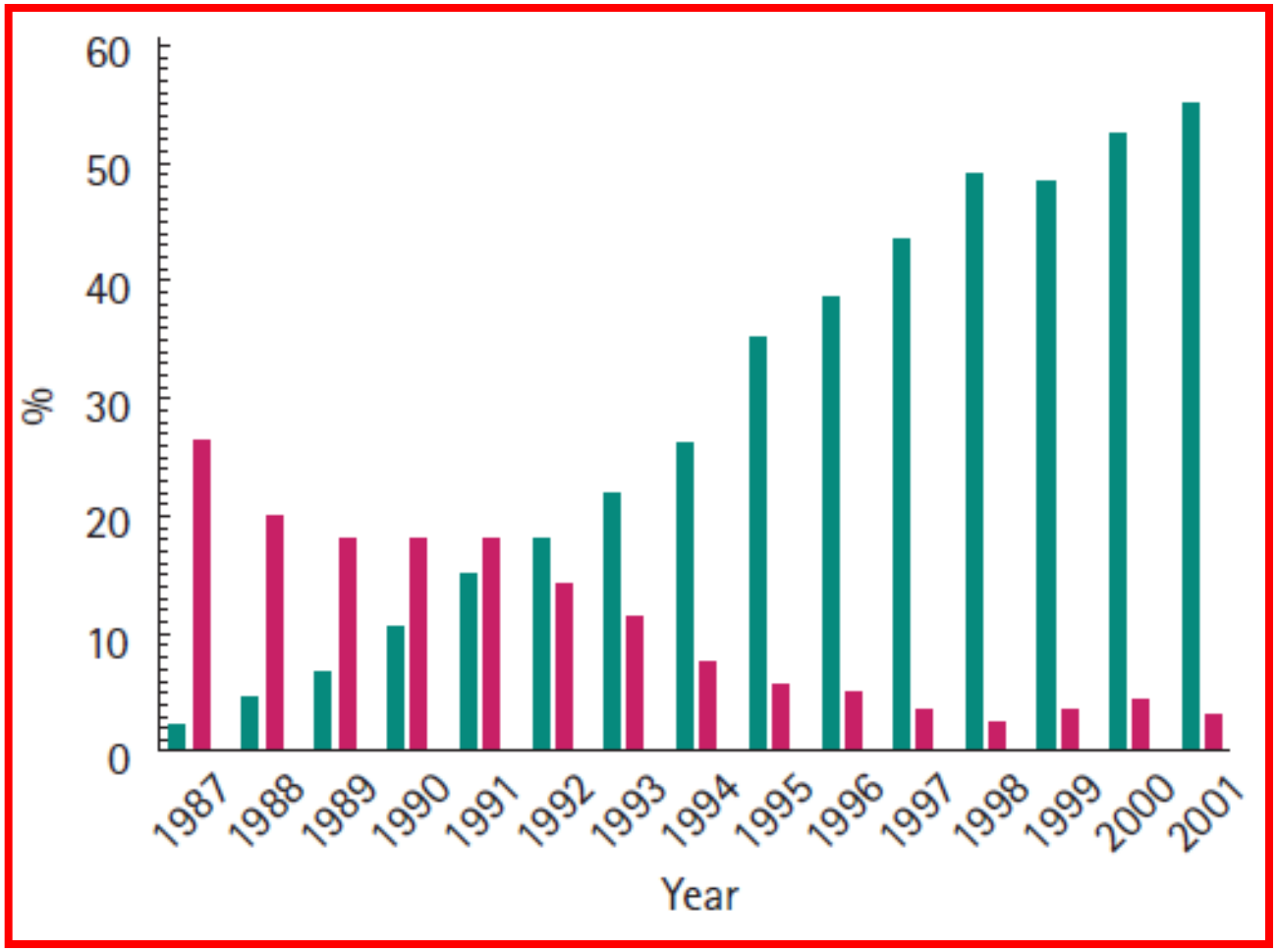
Estimated Deaths

Males

Lung & bronchus	85,920	27%
Prostate	26,120	8%
Colon & rectum	26,020	8%
Pancreas	21,450	7%
Liver & intrahepatic bile duct	18,280	6%
Leukemia	14,130	4%
Esophagus	12,720	4%
Urinary bladder	11,820	4%
Non-Hodgkin lymphoma	11,520	4%
Brain & other nervous system	9,440	3%
All Sites	**314,290**	**100%**

Siegel R et al. Cancer Statistics 2016
Cancer J Clin 2016;66:7-30

PCa stage migration



T1c

T3

T1c

PSA increase

No nodule

Bioptic detection

BJU Int 2005;95:751-6

Lo scenario in Italia

Ogni anno vengono diagnosticati circa **36.000 nuovi casi di tumore della prostata**. E' la neoplasia più frequente tra gli uomini, rappresentando **oltre il 20% di tutti i tumori diagnosticati negli over 50**, ma anche quella caratterizzata da **elevata eterogeneità clinica**, comprendendo casi a bassa aggressività, circa il 30%, tali da essere candidabili ad un programma di sorveglianza attiva e forme clinicamente importanti.

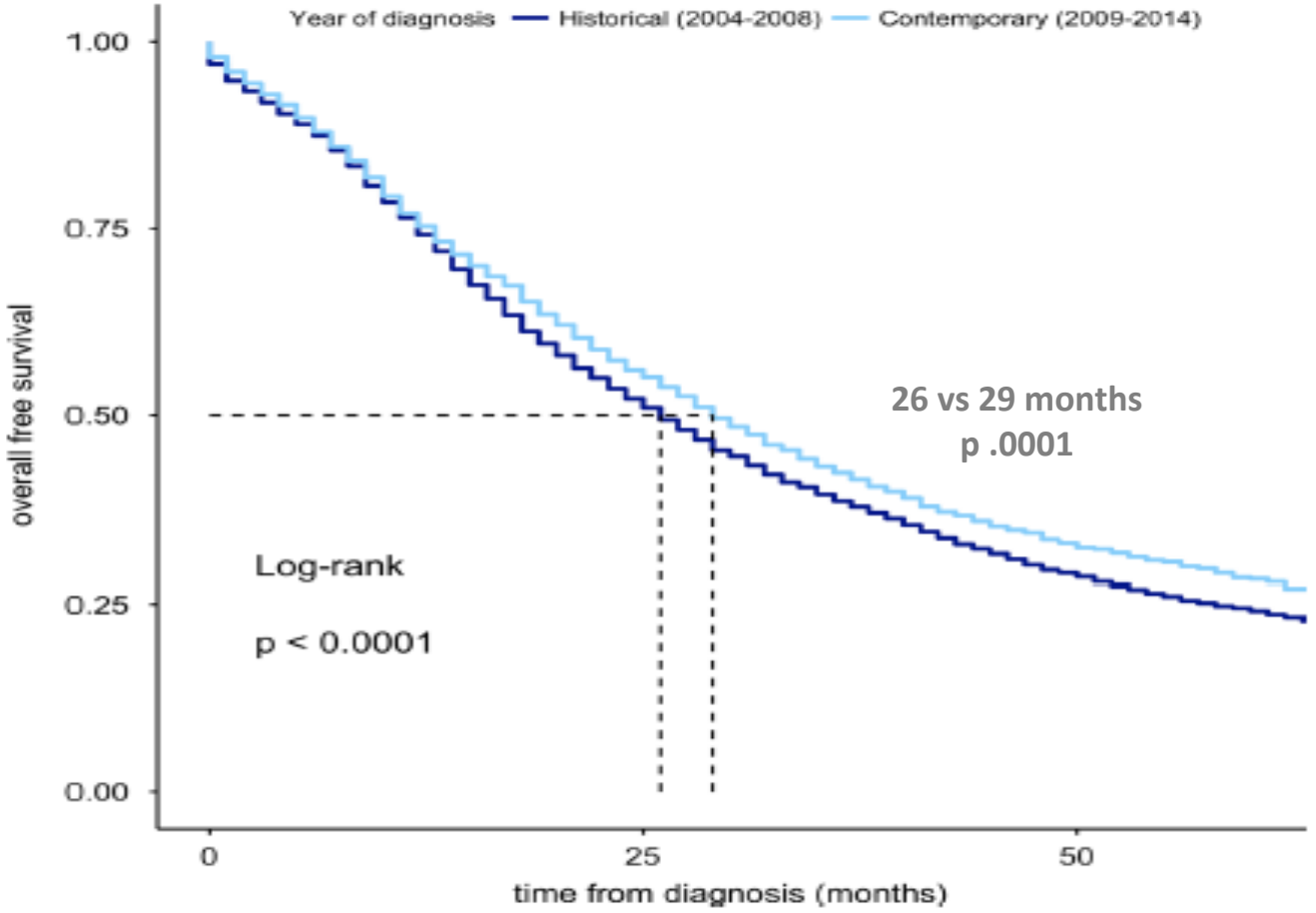
- DHT is the primary prostatic androgen and promotes the growth and survival of normal, hyperplastic and malignant prostate tissues ⟶

- Historically, depleting or blocking the action of the androgens was the only therapeutic solution for patients with metastatic prostate cancer (mPCa);

- Resistance to these therapies occurred in most patients, with the result that the median survival among patients with mCRPCa was approximately 3 years;

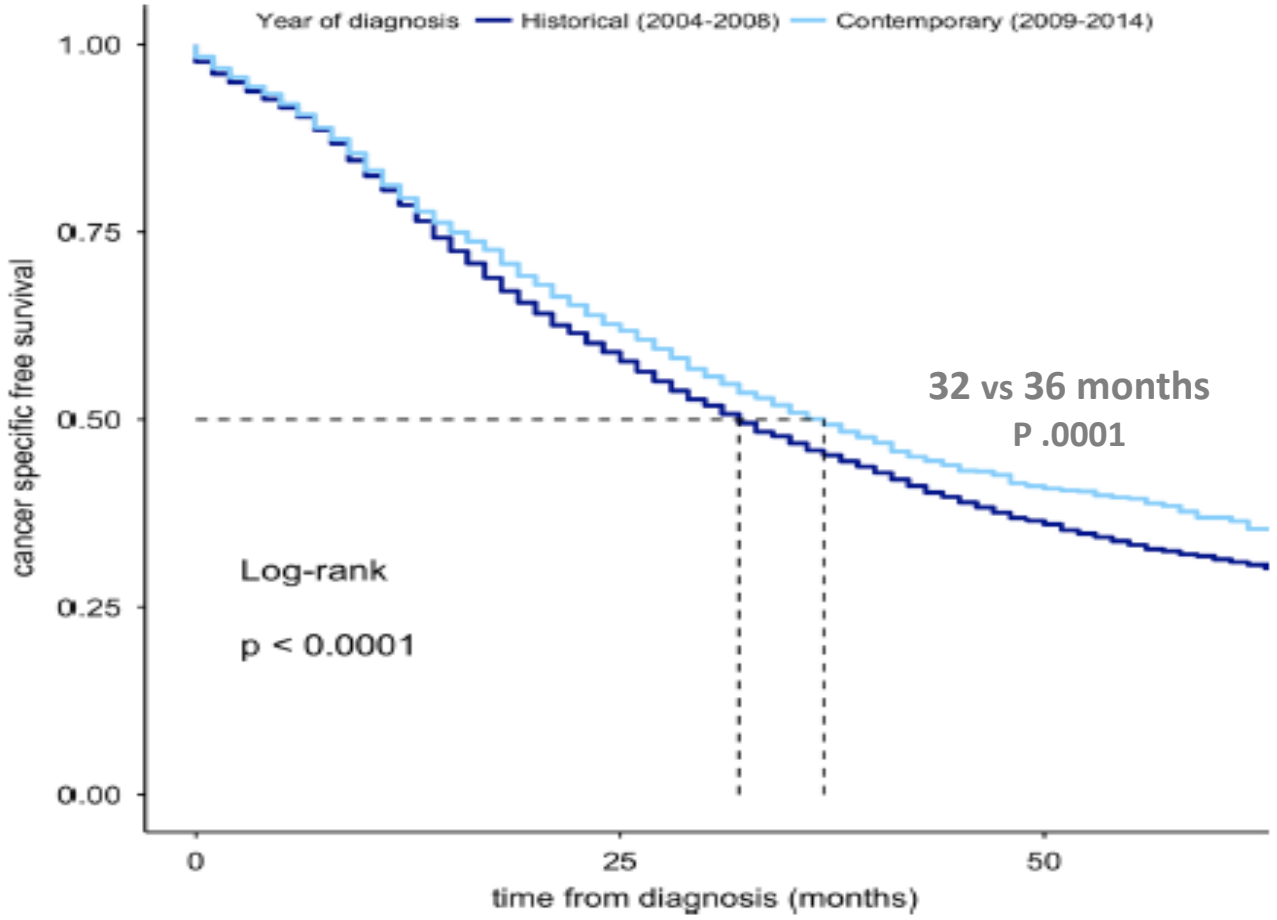
- Over the past decade five agents have been approved based on OS benefit in phase 3 trials. Specifically, these consist of docetaxel (2004), cabazitaxel (2010), sipuleucel-T (2010), abiraterone (2011) and enzalutamide (2012).

Overal survival of 8596 pts with mPC according to the period of diagnosis (2004-2008 vs 2009-2014) from the Surveillance Epidemiology and End Results database



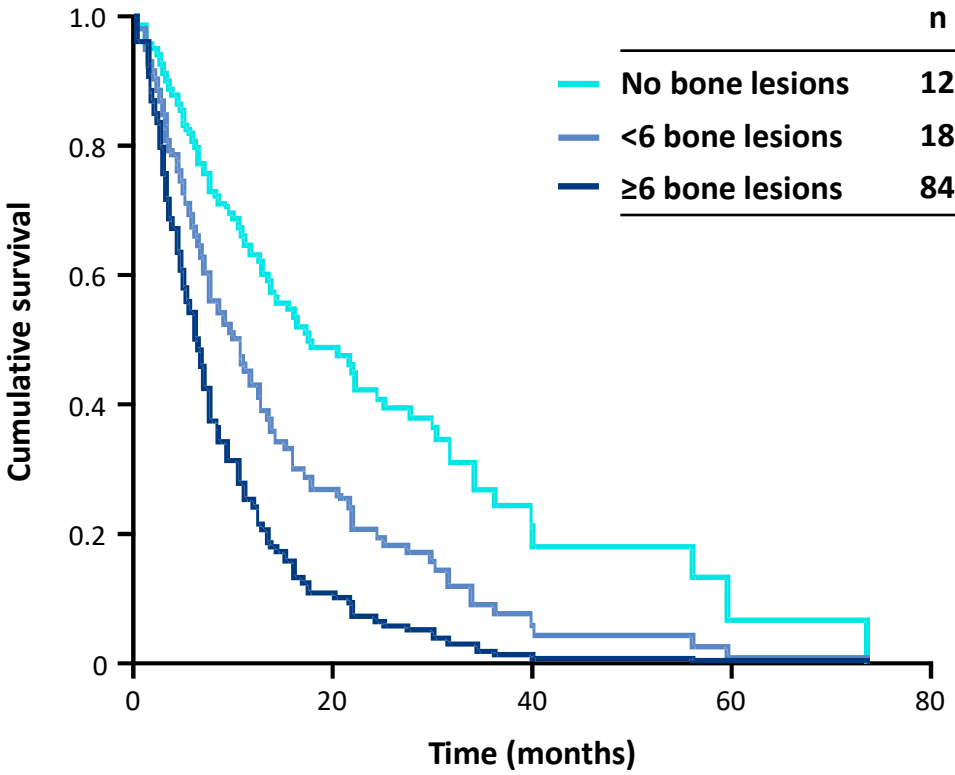
Int Urol Nephrol
DOI 10.1007/s11255-017-1744-2

CSM free survival of 8596 pts with mPC according to the period of diagnosis (2004–2008 vs 2009–2014) from the Surveillance Epidemiology and End Results database



Int Urol Nephrol
DOI 10.1007/s11255-017-1744-2

Extent of bone lesions is associated with increased mortality - CRPC



	n	Median OS, months
No bone lesions	12	18.2
<6 bone lesions	18	8.1
≥6 bone lesions	84	6.1

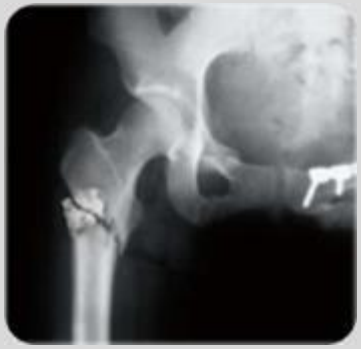
OS, overall survival

Eur Urol 2014;65:270–3

Clinical consequences of bone metastases above the excess of mortality

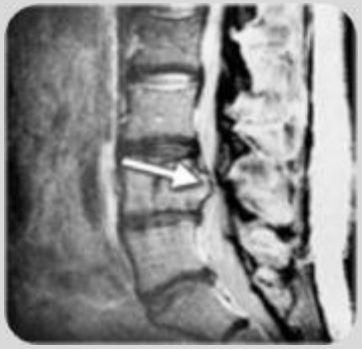
Palliative radiation to bone

29%*



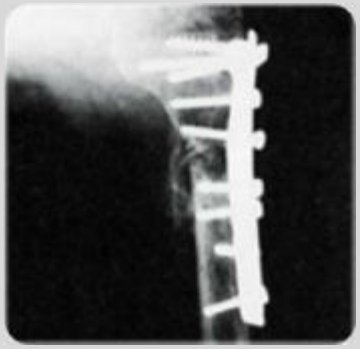
Pathological fracture

22%*



Spinal cord compression

7%*



Surgery to bone

3%*

- Increased pain
- Decreased mobility
- Increased hospitalization

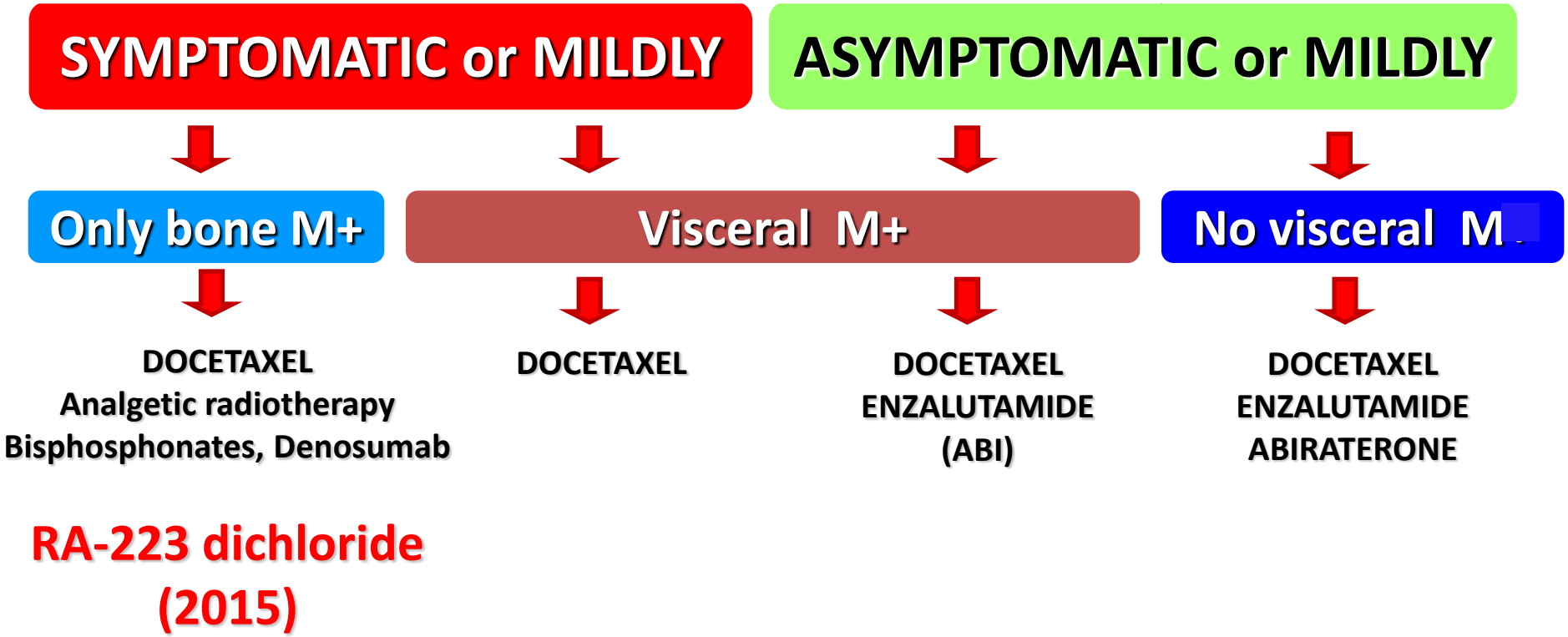
→ Increase in cost, morbidity, and mortality;

Decreased quality of life

*data from the placebo arm of a randomized clinical trial; N=208

Saad F et al. Clin Genitourin Cancer 2007;5:390–6

mCRPC medical treatment up to 2015

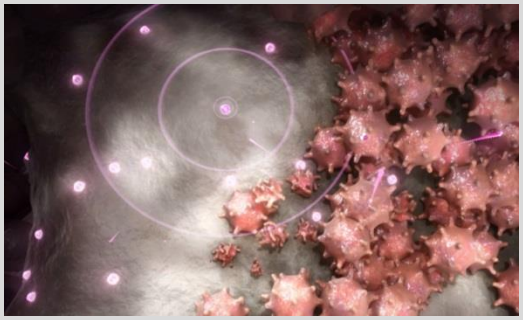


Radium-223 dichloride (Xofigo®): Mechanism of Action

Mimics Calcium

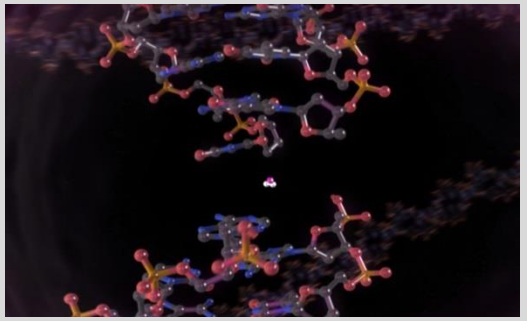
Xofigo **mimics calcium**, forming complexes with the bone **mineral hydroxyapatite at areas of increased bone turnover** such as bone metastases

Short Range



The **short range of alpha particles** emitted by Xofigo (<10 cell diameters) **limits damage to surrounding normal tissue (< 100 µm)**

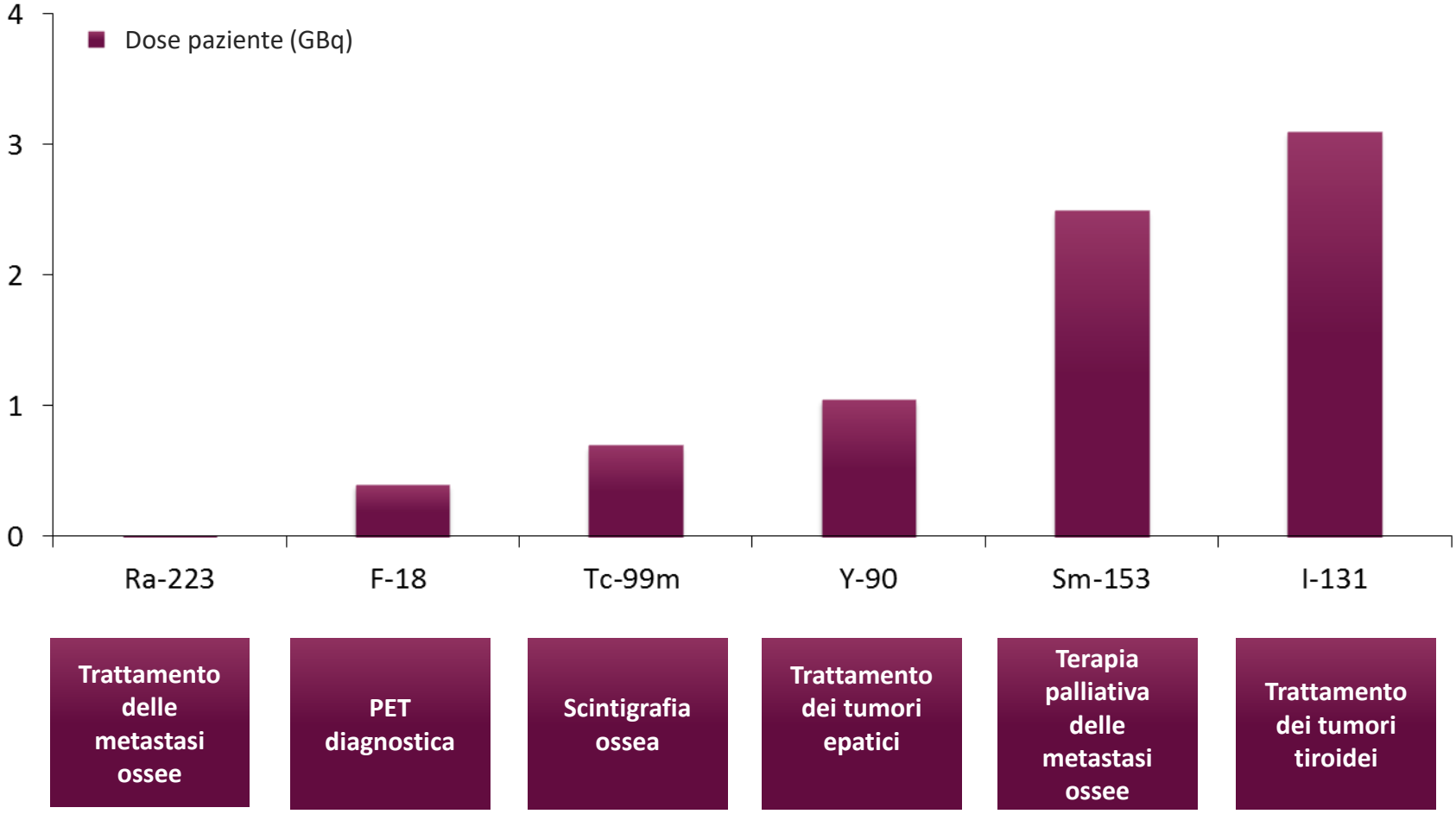
High Linear Energy transfer



Xofigo emits **alpha particles** that **predominantly cause double-strand DNA breaks** in adjacent cells, resulting in an **antitumor effect on bone metastases**

Henriksen, et al. Journal of Nuclear Medicine 44.2 (2003): 252-259

Radio-223 emette una radioattività più bassa rispetto a quella di altri radiofarmaci di uso comune



Radio-223 viene somministrato in Medicina Nucleare

✓ **6 dosi ev ogni 28 giorni**

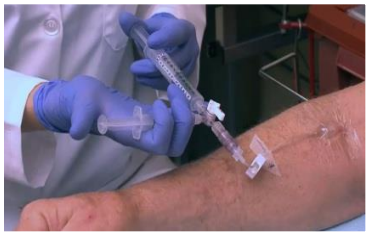
Step 1 Calcolare la dose paziente

Step 2 Aspirare nella siringa

Step 3 Confermare l'attività corretta attraverso la misura nel calibratore

Step 4 Somministrare al paziente

Step 5 Misurare con il calibratore l'attività residua nella siringa



Soluzione fisiologica ev pre- e post-infusione di Ra-223

$$\text{Volume da iniettare (mL)} = \frac{\text{Peso corporeo (kg)} \times 55\ \text{kBq/kg di peso corporeo}}{\text{DK} \times 1100\ \text{kBq/mL}}$$

Esposizione di terzi

Radio-223 raggiunge immediatamente il bersaglio dopo la somministrazione endovenosa:

Circa il 60% dell'attività iniettata viene captata dall'osso entro 4 ore

L'escrezione avviene per lo più attraverso le feci

Circa il 75% viene escreto entro 1 settimana

L'escrezione urinaria è < 5%

Contaminazione e assorbimento dell'attività sono molto improbabili;

Per familiari e caregiver l'esposizione alle radiazioni è trascurabile;

Pazienti: limitazioni minime, misure di igiene standard.

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*

6 injections at 4-week intervals

n=921 mCRPC

Randomization 2:1

Radium 223 + best standard of care

Placebo + best standard of care

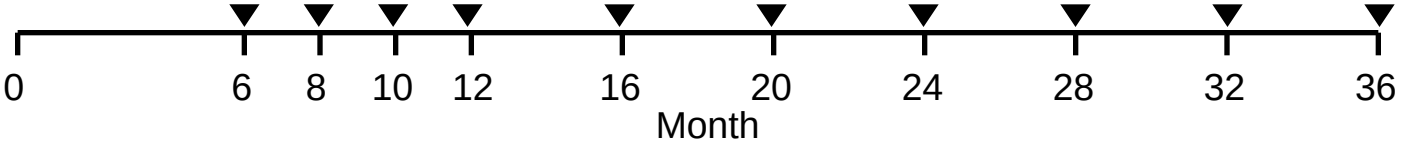
Key inclusion criteria

- Confirmed symptomatic CRPC
- ≥ 2 bone metastases
- No known visceral metastases
- Post-docetaxel or unfit for docetaxel

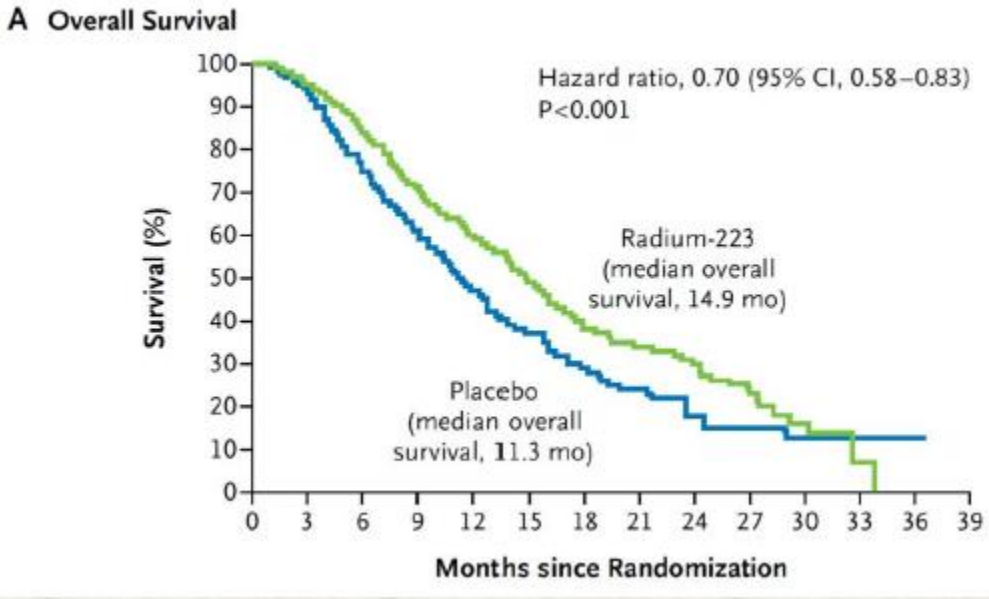
Stratification factors

- Total ALP < 220 U/L vs ≥ 220 U/L
- Bisphosphonate use (Yes vs No)
- Prior docetaxel (Yes vs No)

Assessments

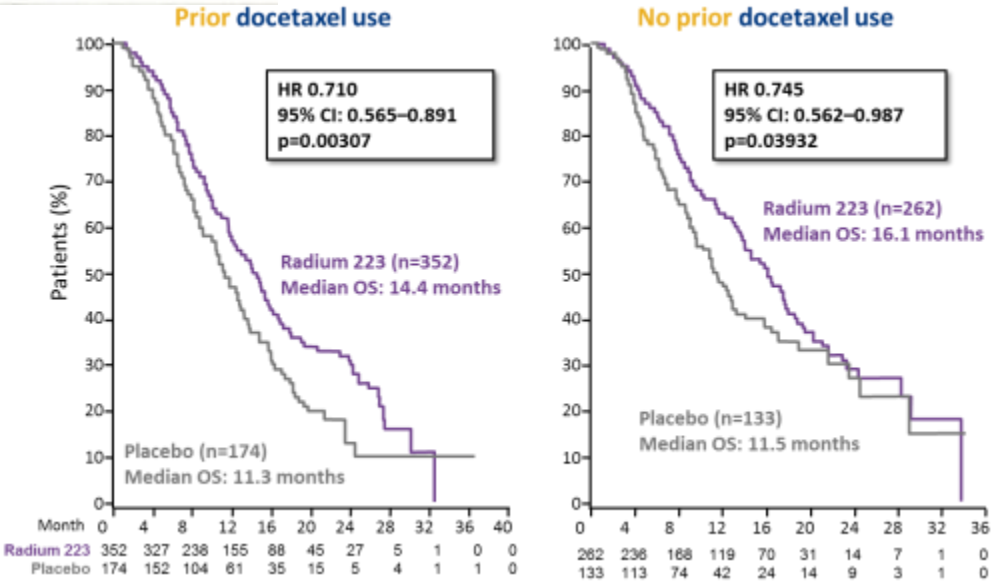


Primary endpoint: overall survival



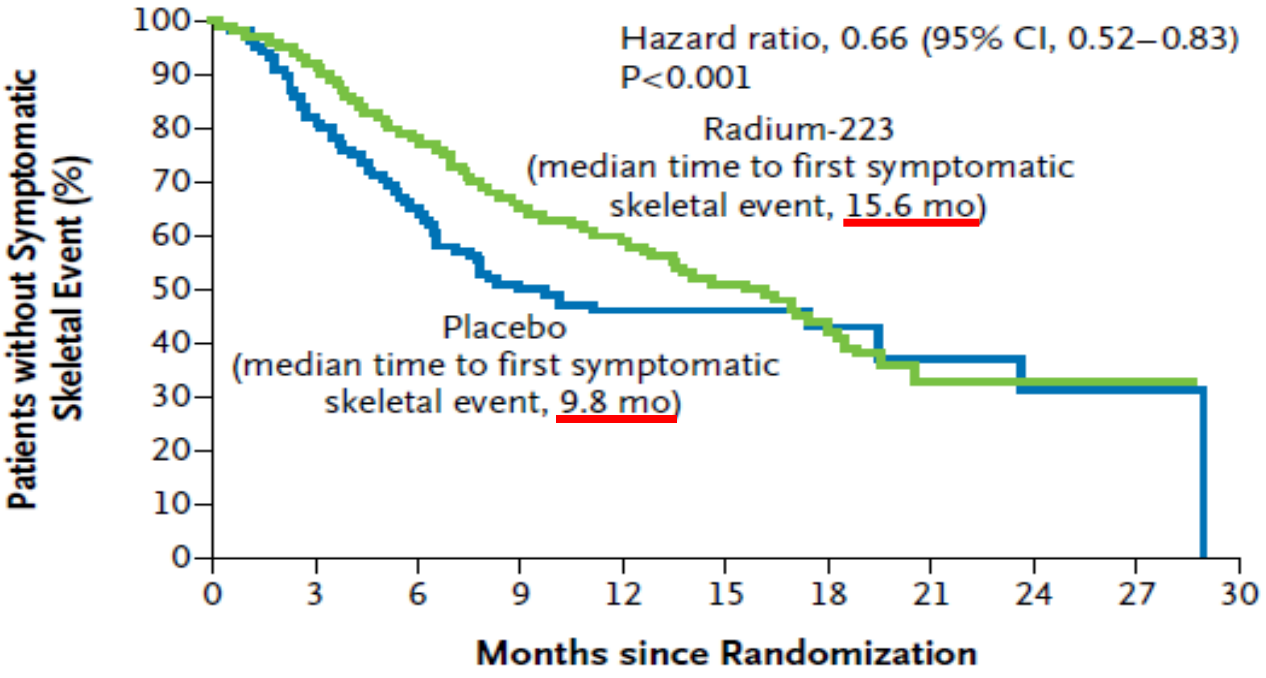
Riduzione del 30% del rischio di morte

Efficacia sia pre- che post-docetaxel



LANCET *Oncol.* 2014;15:1397-406 .

Kaplan–Meier Estimates of the Time to the First Symptomatic Skeletal Event (secondary endpoint)



No. at Risk											
Radium-223	614	496	342	199	129	63	31	8	8	1	0
Placebo	307	211	117	56	36	20	9	7	4	1	0

nejm.org july 18, 2013

Main Secondary Efficacy End Points

End Point	Radium-223 (N=614)	Placebo (N=307)	Hazard Ratio (95% CI)	P Value
Median time to first symptomatic skeletal event — mo	15.6	9.8	0.66 (0.52–0.83)	<0.001
Median time to increase in total alkaline phosphatase level — mo	7.4	3.8	0.17 (0.13–0.22)	<0.001
Patients with ≥30% reduction in total alkaline phosphatase response — no. /total no. (%)	233/497 (47)	7/211 (3)		<0.001
Patients with normalization of total alkaline phosphatase level — no./total no. (%)*	109/321 (34)	2/140 (1)		<0.001

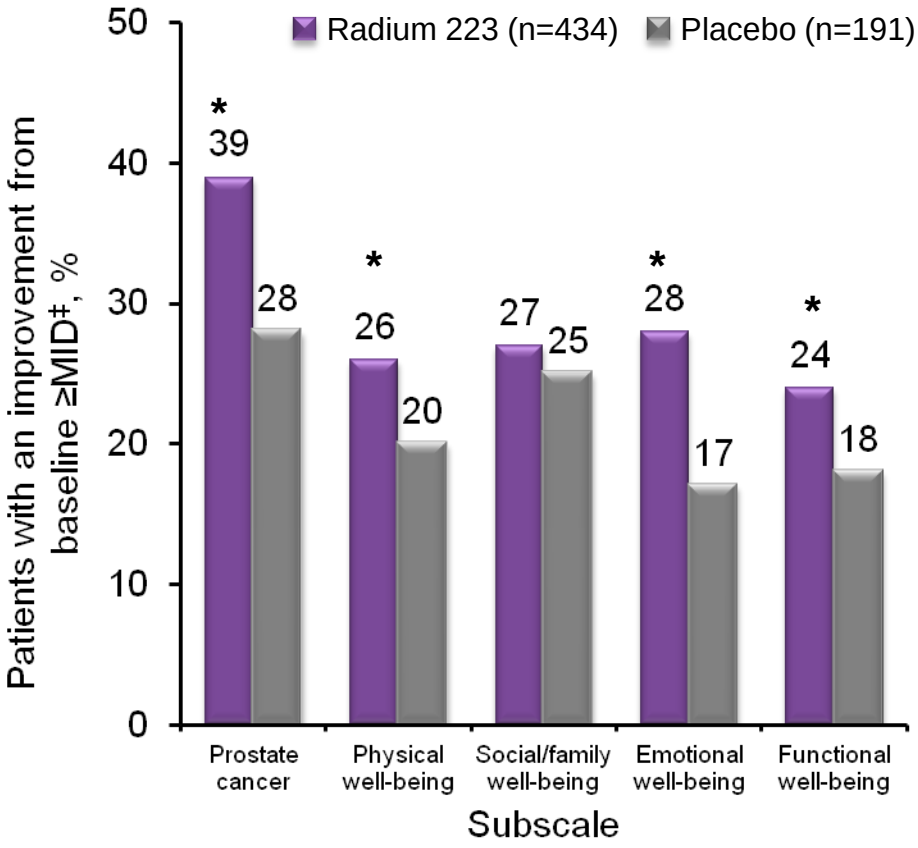
* Only patients who had elevated total alkaline phosphatase levels at baseline are included.

nejm.org july 18, 2013

ALSYMPCA: Quality of Life

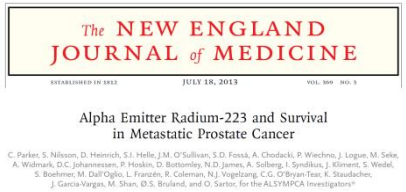
- **Radium-223 significantly improved the QoL response rate vs placebo (27% vs 18%, respectively; P<0.05);**
- **Radium-223 preserved QoL significantly better than placebo, based on FACT-P total score (P=0.006);**
- **Radium-223 improved pain-related quality of life, and reduced the incidence of bone pain as an adverse event.**

FACT-P subscale scores



*p<0.05; FACT-P, Functional Assessment of Cancer Therapy-Prostate

Parker C et al. ESMO 2012 Poster presentation 898PD.



Phase 3 ALSYMPCA: adverse events

	All Grades		Grades 3 or 4	
	Radium 223 (n=600)	Placebo (n=301)	Radium 223 (n=600)	Placebo (n=301)
HAEMATOLOGICAL				
Anaemia	187 (31)	92 (31)	77 (13)	40 (13)
Neutropenia	**30 (5)**	**3 (1)**	**13 (2) 1./500**	**2 (1)<500**
Thrombocytopenia	**69 (12)**	**17 (6)**	**3 (6)50./25.000**	**6 (2)<25.000**
NON-HAEMATOLOGICAL				
Bone pain	300 (50)	187 (62)	125 (21)	77 (26)
Diarrhoea	**151 (25)**	**45 (15)**	**9 (2)**	**5 (2)**
Nausea	213 (36)	104 (35)	10 (2)	5 (2)
Vomiting	111 (19)	41 (14)	10 (2)	7 (2)
Constipation	108 (18)	64 (21)	6 (1)	4 (1)

Data are n (%)

Safety a 3 anni dall'ultima somministrazione del farmaco: punti chiave

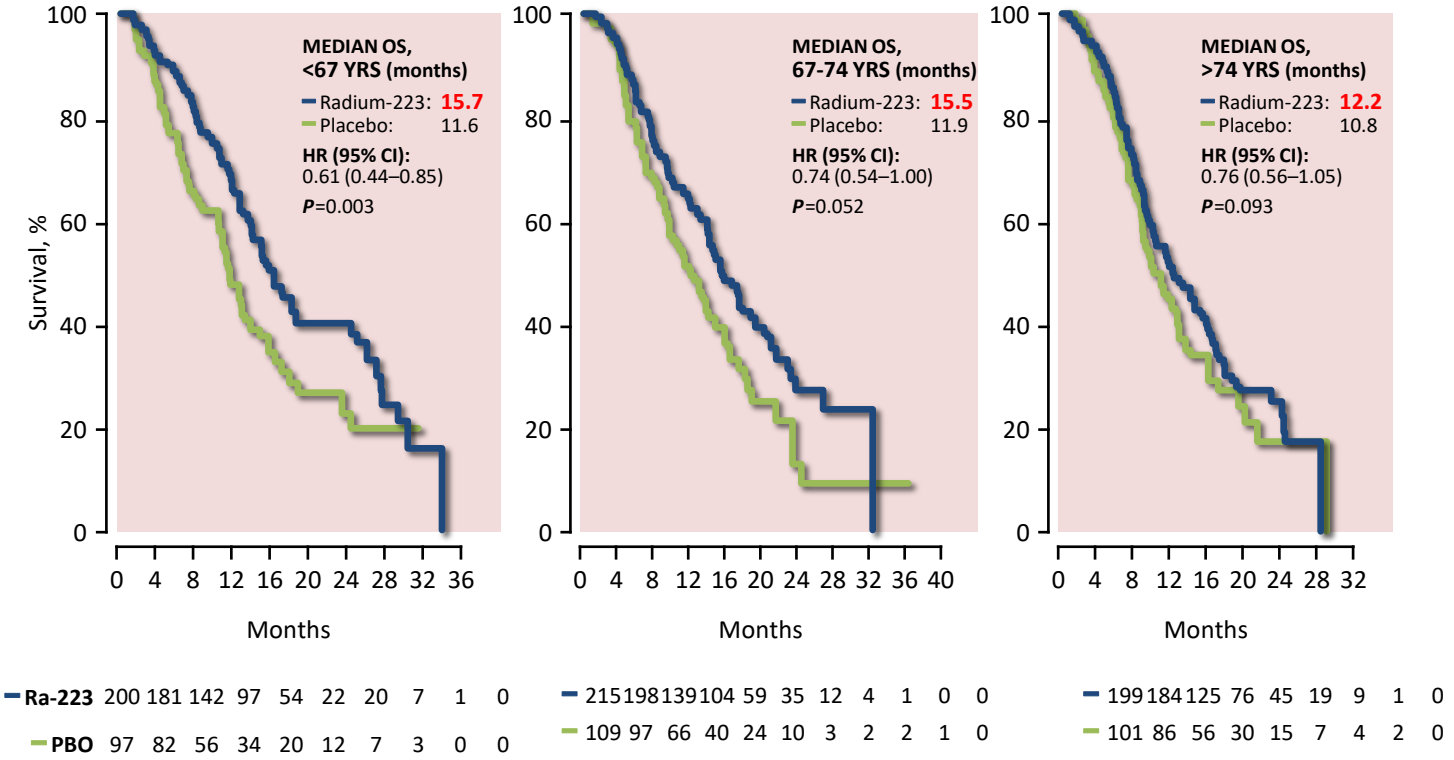
I risultati del follow-up di sicurezza a lungo termine **non hanno evidenziaato nuovi problemi di sicurezza** ed in particolare:

- **L'incidenza della mielosoppressione** nei trattati con Ra-223 **è rimasta stabile** durante l'intero periodo di follow-up;
- Non sono occorsi, sempre nei trattati, **eventi di AML, MDS o tumore osseo primario;**
- Al termine del follow-up (totale 42 mesi) **erano in vita il 14% dei pazienti trattati con Ra-223 ed il 7% di quelli con placebo.**

Parker et al. Eur Urol (2017)

Overall Survival Ra-223 vs Placebo in All Age Groups

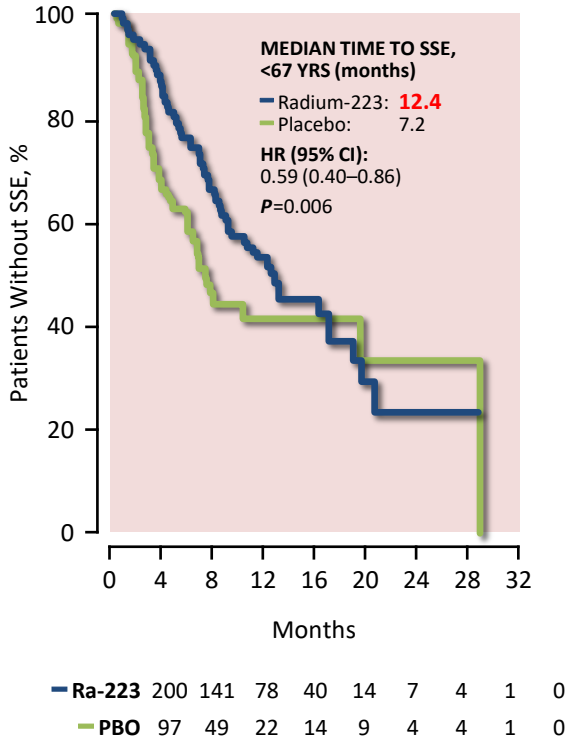
ALSYMPCA ITT population (921 patients) Radium-223 significantly improved OS compared to placebo: median, 14.9 months vs. 11.3 months; HR=0.70, 95% CI, 0.58 to 0.83; P<0.001

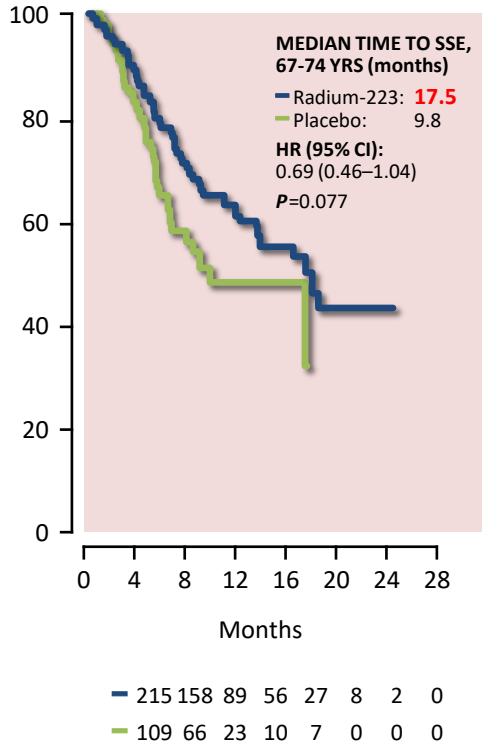


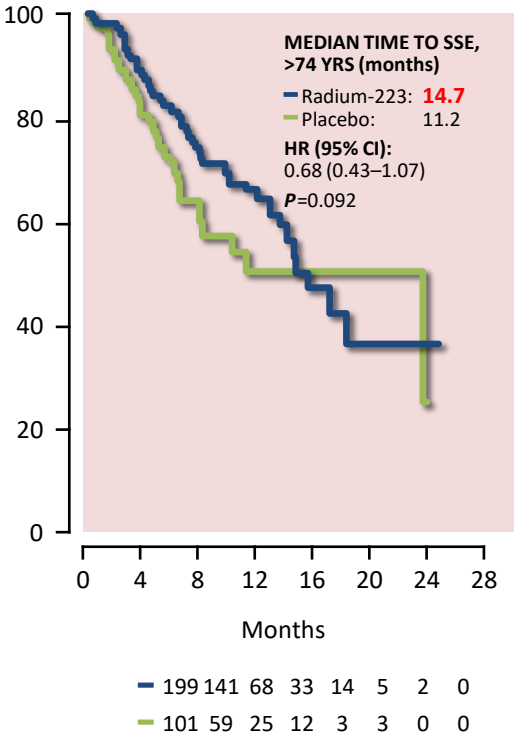
Wiechno P, et al. Ann Oncol. 2013;49 (suppl 2; abstr 2883)

Time to First Symptomatic Skeletal Event Ra-223 vs Placebo in All Age Groups

ALSYMPCA ITT population (921 patients) Radium-223 prolonged the time to the first SSE: median, 15.6 months vs. 9.8 months; HR=0.66, 95% CI, 0.52 to 0.83; P<0.001

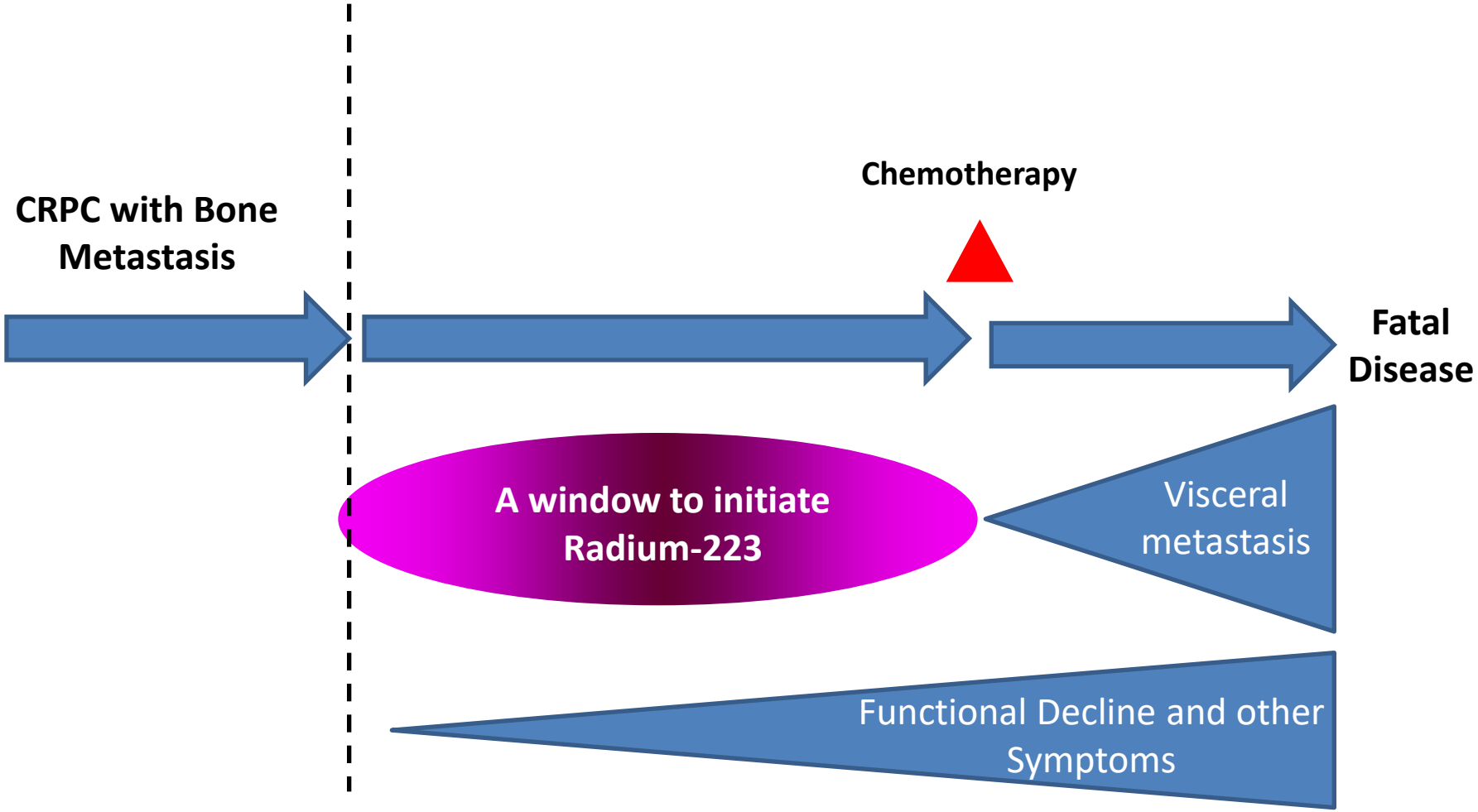






Wiechno P, et al. Ann Oncol. 2013;49 (suppl 2; abstr 2883)

Radium-223: Patient Selection



Ryan et al N Engl J Med 2013;368:138-48
Beer et al N Engl J Med. 2014 Jul 31;371(5):424-33
Pezaro et al Eur Urol 2014

Ra-223: Take Home Messages

- **Meccanismo d'azione non sovrapponibile con altri farmaci;**
- **Consente il successivo impiego di chemioterapia;**
- **E' efficace:**
  - **Incremento della sopravvivenza**
  - **Riduce gli eventi scheletrici**
  - **Contiene il dolore**
- **E' ben tollerato;**
- **Non presenta tossicità importanti:**
  - **In pazienti > 70 anni, in cui possono coesistere squilibri elettrolitici, disturbi cardiocircolatori, disidratazione**
  - **In pazienti con PS scaduto**
  - **In pazienti con insufficienza renale o insufficienza epatica.**

Centri con Nulla Osta in Italia

(21-11-2017)

- **85 Centri con Nulla Osta per Ra223**
- **70 centri hanno trattato pazienti**
- **Circa 1200 pazienti trattati**