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UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena
Policlinico

Il Trattamento della Malattia CRPC metastatica

Terapie Radiometaboliche

Roberto Sabbatini
Azienda Ospedaliero Universitaria
Policlinico di Modena

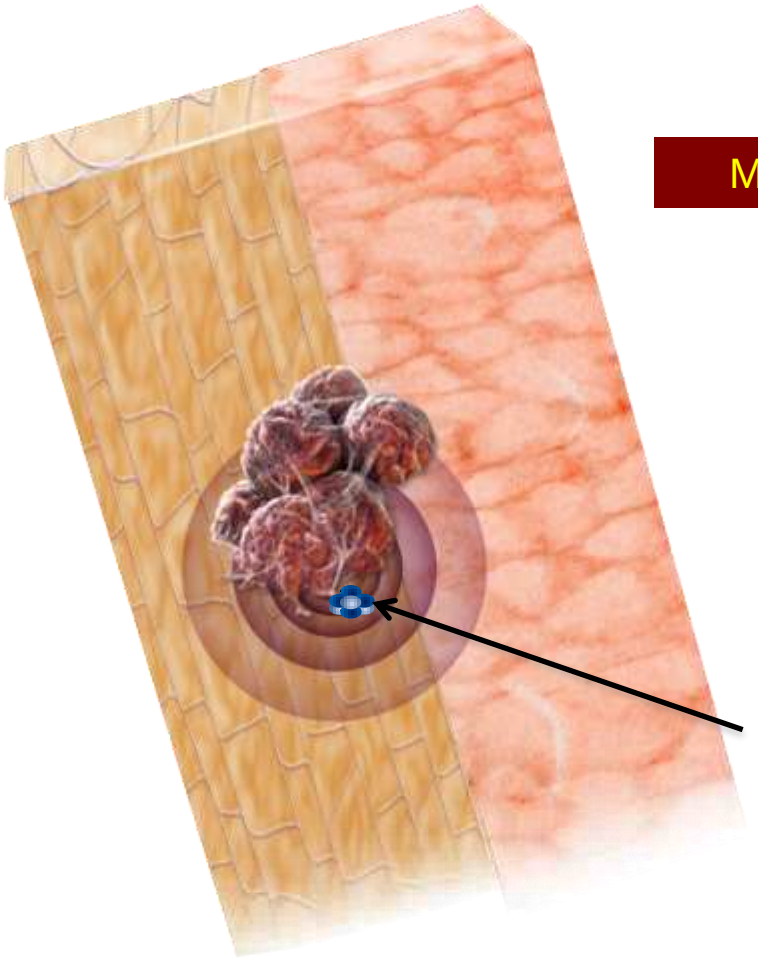
AIOM: Gestione ottimale del Paziente con Carcinoma della Prostata
Milano, 25-26 Settembre 2018

iGO
INNOVATORS IN GENITO-URINAY ONCOLOGY

Efficacy of Therapies for Metastatic Castration-resistant Prostate Cancer Patients

Therapy	Comparator	Improvement in mOS (mos) vs comparator	Hazard ratio
Enzalutamide			
Pre-chemo	Placebo	4.0	0.77
Post-chemo	Placebo	4.8	0.63
Cabazitaxel	Mitoxantrone	2.4	0.70
Abiraterone			
Pre-chemo	Placebo	4.4	0.81
Post-chemo	Placebo	4.6	0.74
Docetaxel	Mitoxantrone	2.4	0.76
Sipuleucel-T	Placebo	4.1	0.78
Radium-223 plus BSC	**Placebo plus BSC**	**3.6**	**0.70**

Short Range of α-Emitters Reduces Bone Marrow Exposure



Range of α-particle (short range: 2-10 cell diameters[2])

= highly localised tumour cell killing and minimal damage to surrouding normal tissue

1. Bruland Ø, et al. Clin Cancer Res. 2006;
2. Henriksen G, et al. Cancer Res. 2002;

Cell killing and marrow penetration: Two advantages of α-emitters

Large molecule
+
High Linear Energy Transfer

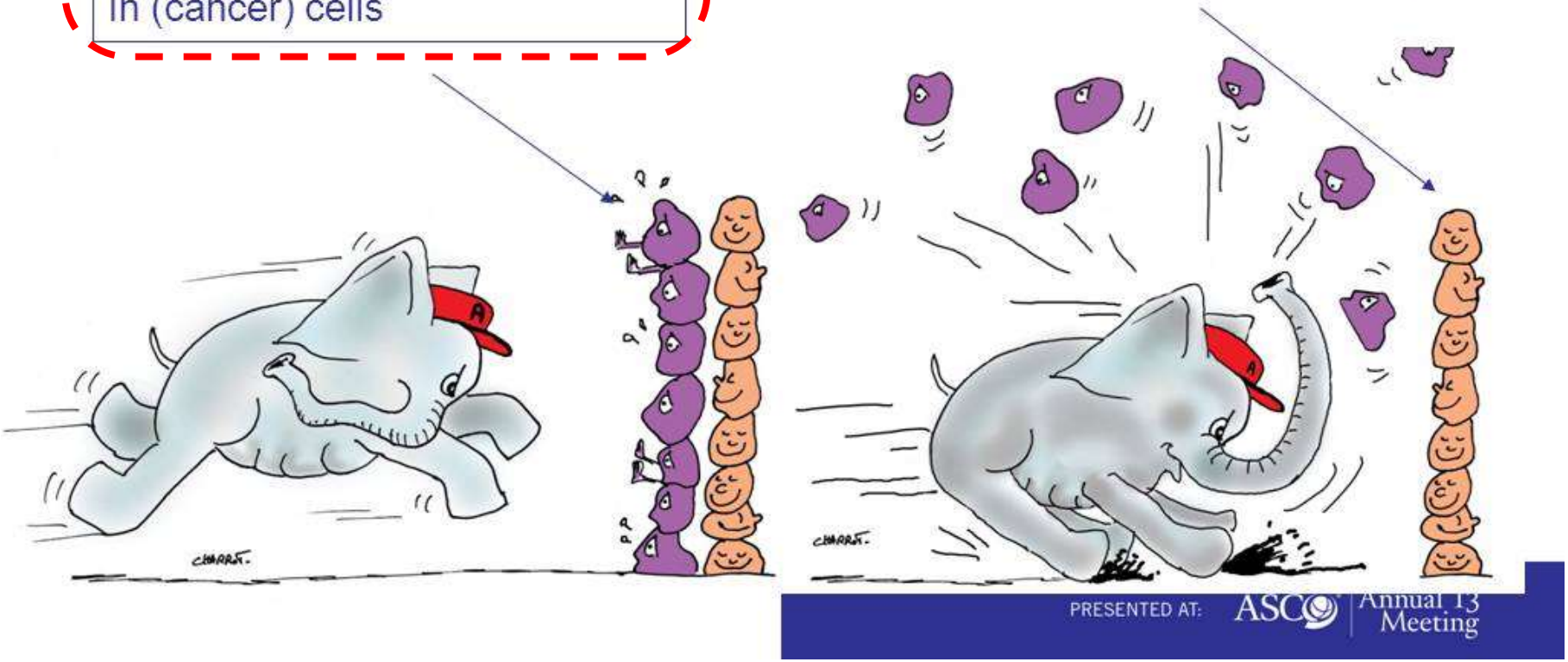
▼

More DNA double-strand breaks
In (cancer) cells

Low marrow penetration (≤100 µm)

▼

Limited hematological toxicity



PRESENTED AT: ASCO Annual 13 Meeting

Fizazi K, ASCO 2013

Cell killing and marrow penetration: Two advantages of α-emitters

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↓

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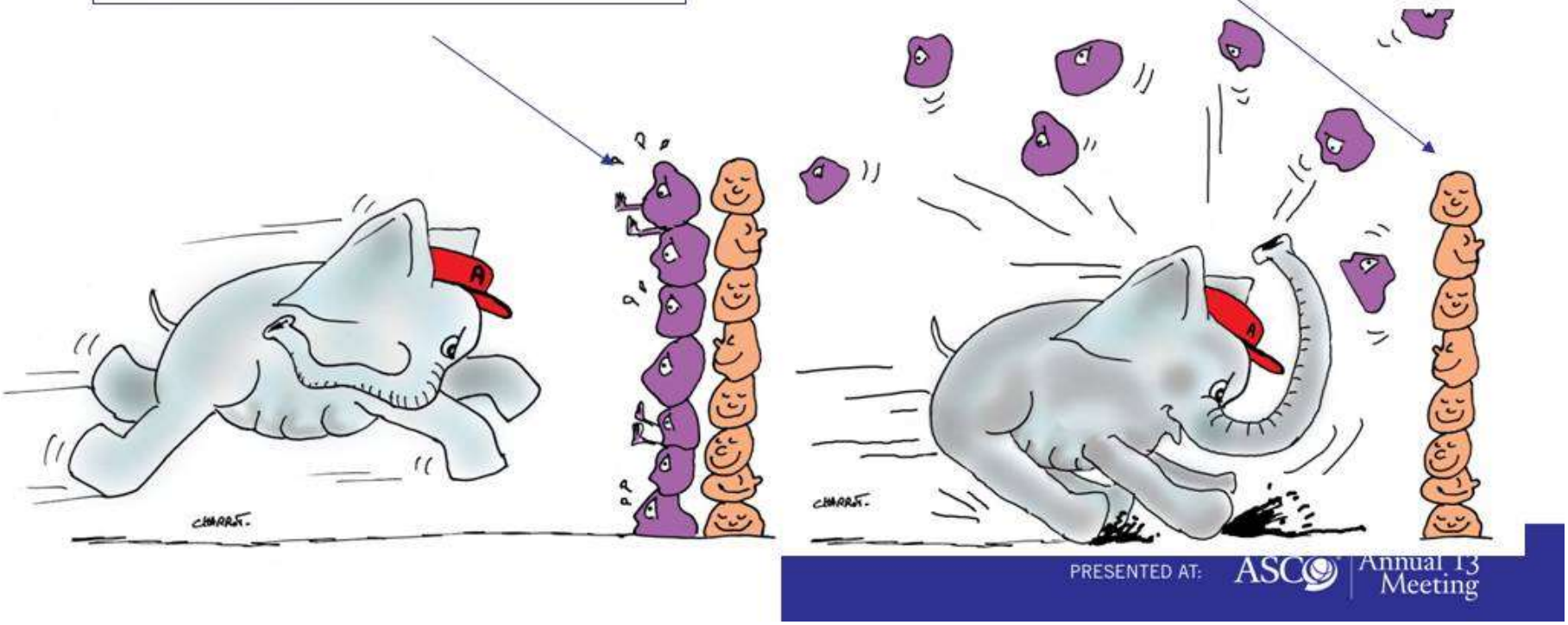
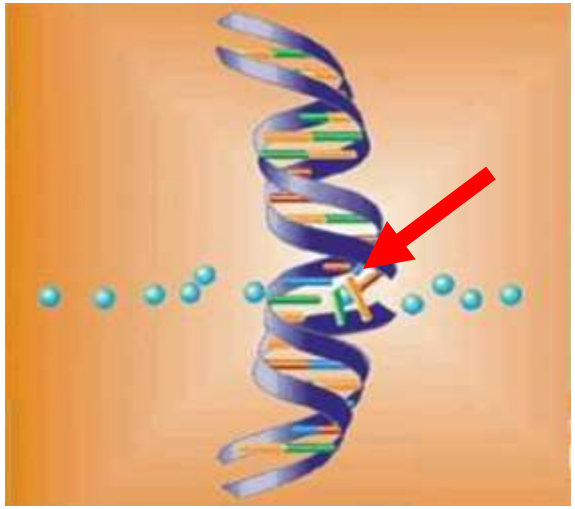


PRESENTED AT: ASCO Annual 13 Meeting

Alpha-Particles Cause Lethal *Double*-Strand DNA Breaks

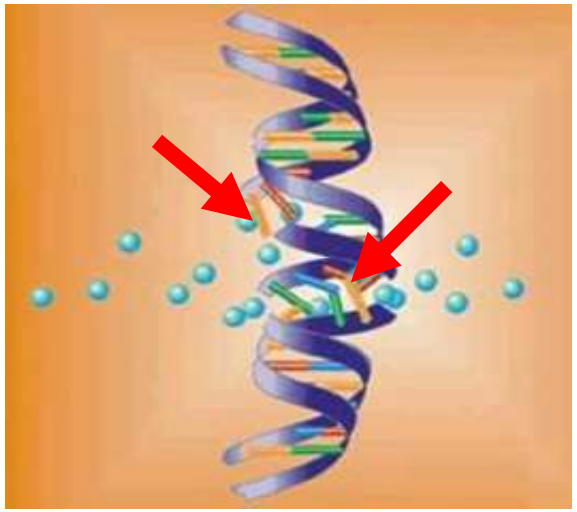
β-emitters



- Low-LET β radiation produces single-strand DNA breaks[1]
- Single-strand breaks are easily repaired using the opposite strand as a template[1]
- Single-strand breaks are less likely to induce cell death[1]

α-emitters

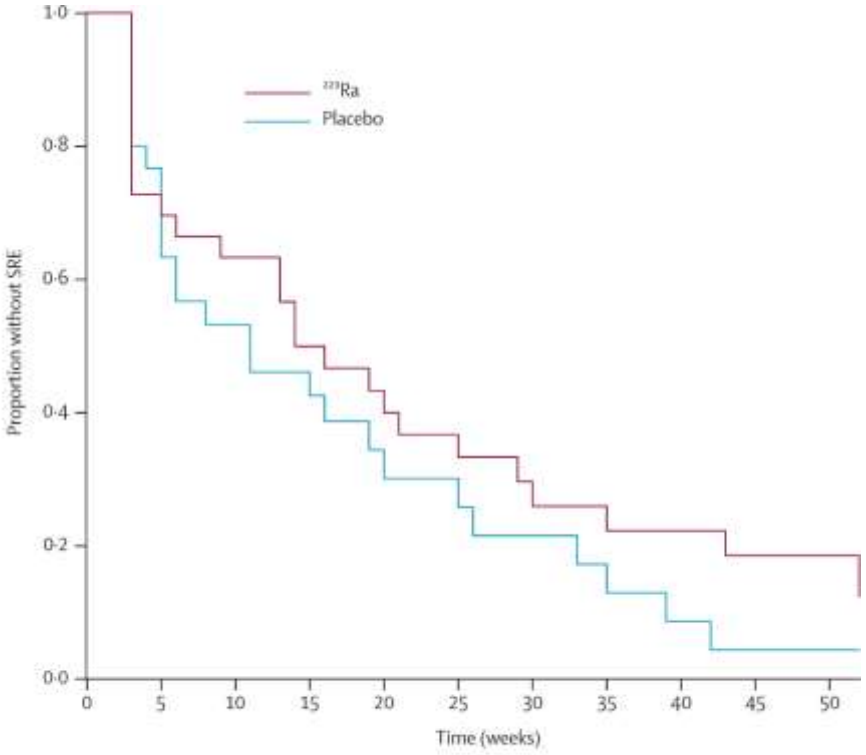
- High-LET α -particles produce double-strand DNA breaks[1,2]
- Double-strand breaks are difficult to repair[1,2]
- Failure to repair double-strand breaks leads to apoptosis (programmed cell death)[1]
- Mis-repaired double-strand breaks create chromosomal aberrations that result in mitotic cell death[1]



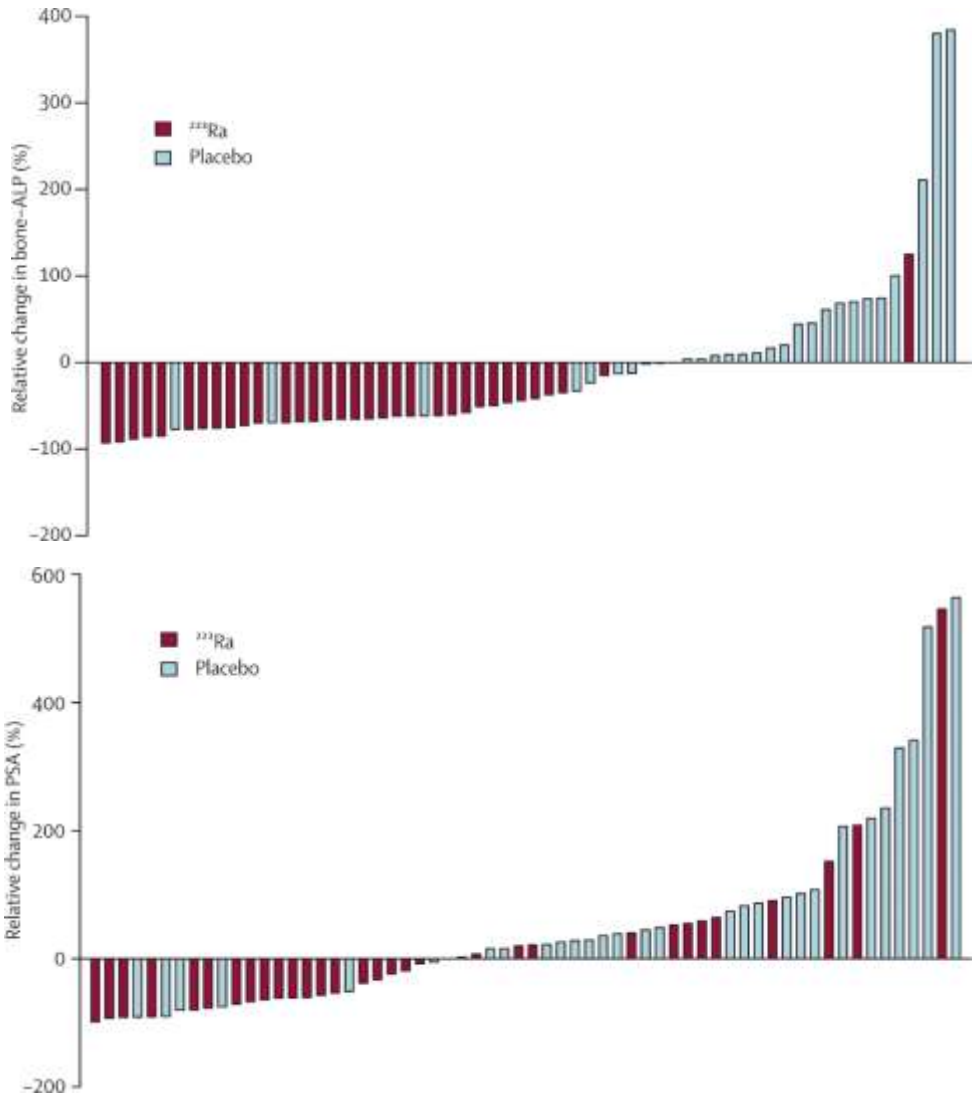
LET, linear energy transfer

1. Hall EJ, Giaccia AJ. Radiobiology for the Radiologist. 6th ed. Philadelphia, PA: Lippincott William & Wilkins; 2006. 2. Bruland OS, et al. Clin Cancer Res. 2006;12(20):6250s-6257s.

Radium-223: Phase II Data in HRPC

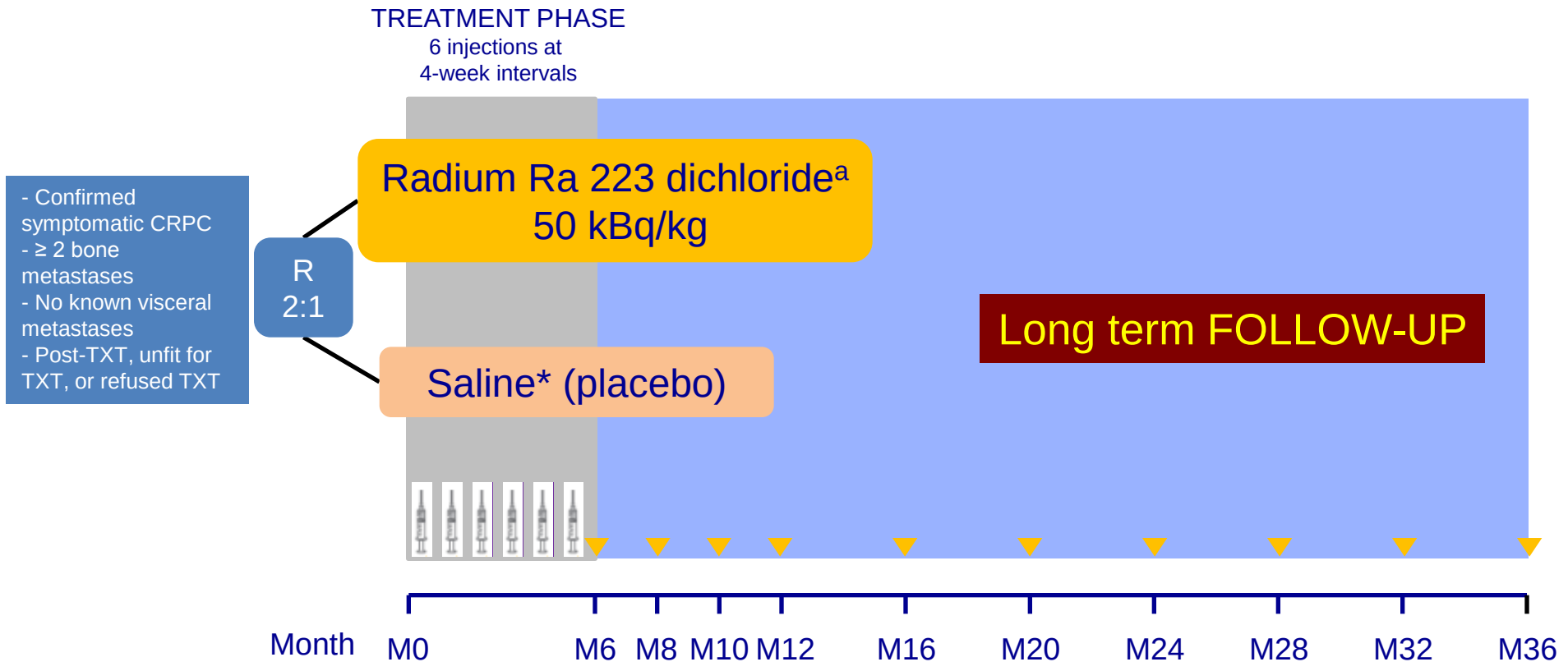


	Radium-223	Placebo	*P* Value
PSA	–24%	+45%	0.003
ALP	–46%	+31%	< 0.0001



Nilsson S, et al. Lancet Oncol. 2007

ALSYMPCA: phase 3, randomized, double-blind, placebo-controlled study



Stratification factors
•Total ALP < 220 U/L vs ≥ 220 U/L; Bisphosphonate use (yes vs no); Prior docetaxel (yes vs no)

Parker C, et al. NEJM 2013.

ALSYMPCA trial: Endpoints

PRIMARY ENDPOINT

- Overall survival

SECONDARY ENDPOINTS

- Time to total ALP progression[a]
- Total ALP response[a]
- Time to occurrence of first SSE
- Total ALP normalization[a,b]
- Time to PSA progression[a,c]
- Other secondary efficacy endpoints[a]
- Safety
- Quality of life

ALP, alkaline phosphatase; PSA, prostate-specific antigen; SSE, symptomatic skeletal event.

a. See slides ("Other Secondary Efficacy Endpoints") for more details.

b. Defined as return of total ALP to within normal range at 12 weeks [confirmed by two consecutive measurements ≥2 weeks apart] in patients with total ALP values above upper limit of normal (ULN) at baseline.

c. Defined as ≥25% increase from baseline and an absolute value increase ≥2 ng/mL at ≥12 weeks [in patients with no PSA decline from baseline] or ≥25% increase and an absolute value increase ≥2 ng/mL above nadir confirmed ≥3 weeks later, in patients with an initial decrease from baseline.

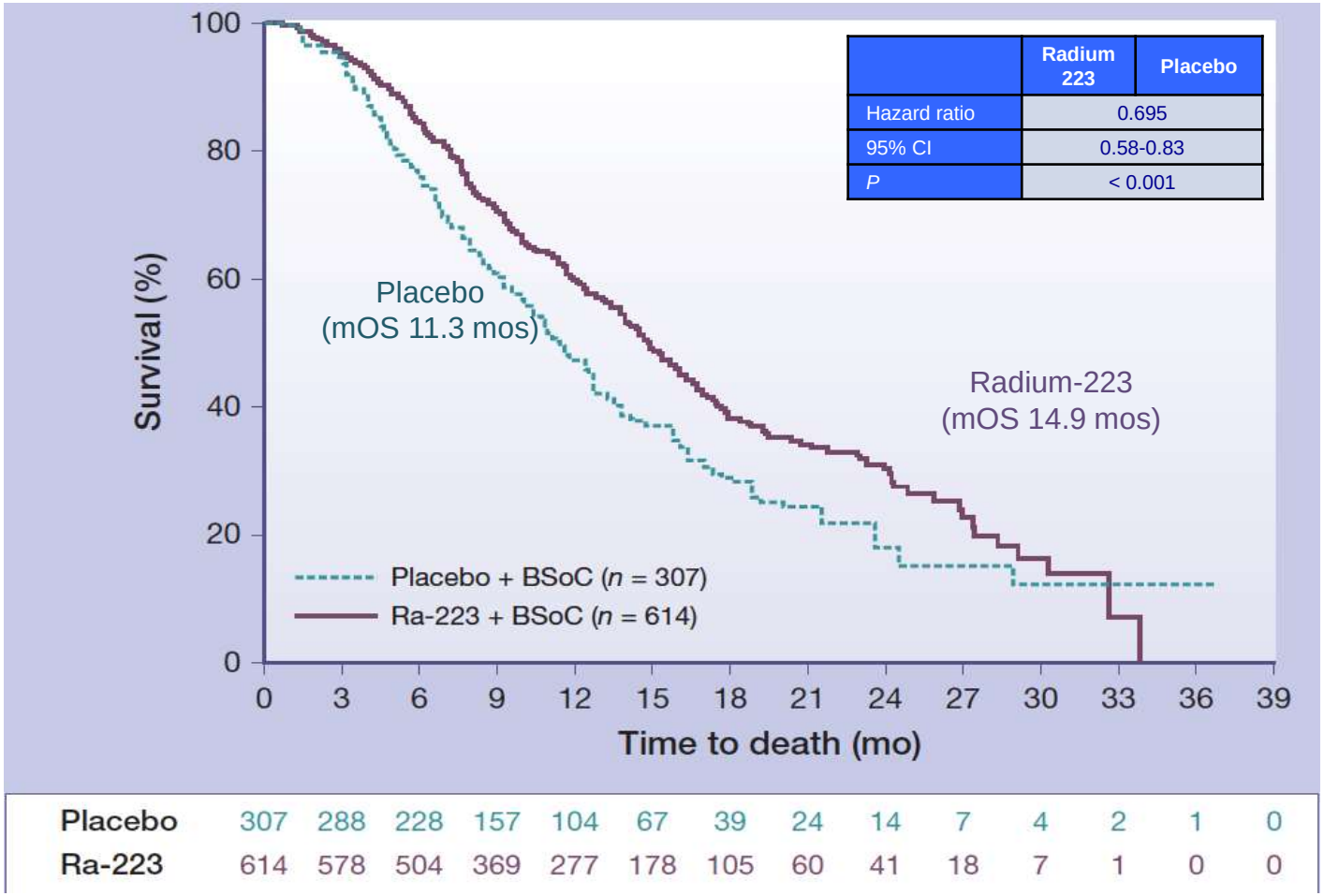
SOURCE: Parker C, et al. *N Engl J Med.* 2013;369(3):213-23.

ALSYMPCA Updated Analysis Patient Demographics and Baseline Characteristics (ITT N = 921)

Parameter	Radium-223 n = 614	Placebo n = 307
Age, y		
Mean	70.2	70.8
Race, n (%)		
Caucasian	575 (94)	290 (95)
Baseline ECOG score, n (%)		
≤ 1	536 (87)	265 (86)
2	76 (12)	40 (13)
Extent of disease, n (%)		
< 6 metastases	100 (16)	38 (12)
6–20 metastases	262 (43)	147 (48)
> 20 metastases/superscan	249 (41)	121 (40)
WHO ladder, cancer pain index ≥ 2, n (%)	345 (56)	168 (55)

Parker C, et al. ASCO 2012

ALSYMPCA trial: Kaplan–Meier Estimates of Overall Survival



	Radium 223	Placebo
Hazard ratio	0.695	
95% CI	0.58-0.83	
P	< 0.001	

Parker C, et al. NEJM 2013

ALSYMPCA Updated Analysis: Safety Profiles Were Similar Between the Radium-223 and Placebo Arms

There were few grade 3 AEs and grade 4 AEs were very low, also comparable to placebo

	RADIUM-223 (n = 600)				PLACEBO (n = 301)			
EVENT	ALL GRADES, n (%)	GRADE 3, n (%)	GRADE 4, n (%)	GRADE 5,[a] n (%)	ALL GRADES, n (%)	GRADE 3, n (%)	GRADE 4, n (%)	GRADE 5,[a] n (%)
Hematologic AEs								
Anemia	187 (31)	65 (11)	11(2)	0	92 (31)	37 (12)	2 (1)	1 (<1)
Thrombocytopenia	69 (12)	20 (3)	18 (3)	1 (<1)	17 (6)	5 (2)	1 (<1)	0
Neutropenia	30 (5)	9 (2)	4 (1)	0	3 (1)	2 (1)	0	0
Nonhematologic AEs								
Constipation	108 (18)	6 (1)	0	0	64 (21)	4 (1)	0	0
Diarrhea	151 (25)	9 (2)	0	0	45 (15)	5 (2)	0	0
Nausea	213 (36)	10 (2)	0	0	104 (35)	5 (2)	0	0
Vomiting	111 (19)	10 (2)	0	0	41 (14)	7 (2)	0	0
Asthenia	35 (6)	5 (1)	0	0	18 (6)	4 (1)	0	0
Fatigue	154 (26)	21 (4)	3 (1)	0	77 (26)	16 (5)	2 (1)	0
General physical health deterioration	27 (5)	9 (2)	2 (<1)	5 (1)	21 (7)	8 (3)	2 (1)	2 (1)
Peripheral edema	76 (13)	10 (2)	0	0	30 (10)	3 (1)	1 (<1)	0
Pyrexia	38 (6)	3 (1)	0	0	19 (6)	3 (1)	0	0
Pneumonia	18 (3)	9 (2)	0	4 (1)	16 (5)	5 (2)	2 (1)	0

Only 1 grade 5 hematologic AE was considered possibly related to study drug: thrombocytopenia in 1 patient in the radium-223 group.

Parker C, et al. *N Engl J Med.* 2013

Safety: Radium-223 Was Well Tolerated Across All Age Groups

Incidence of Grade 3/4 Adverse Events According to Age (Safety Population, N=901*)

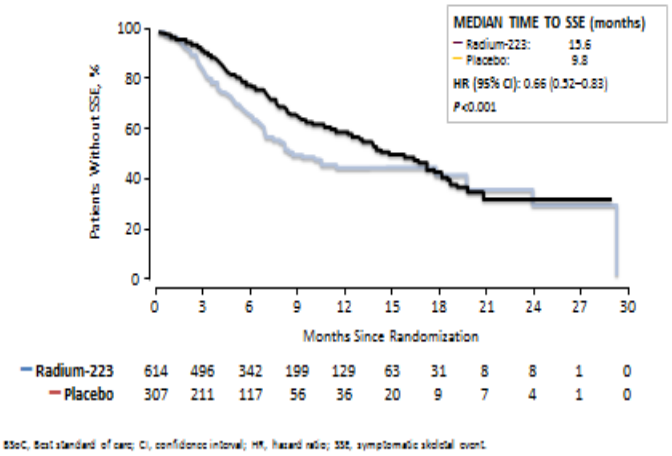
	ALL AGES		<67 YEARS		67-74 YEARS		>74 YEARS	
n (%)	RADIUM-223 n=600	PLACEBO n=301	RADIUM-223 n=194	PLACEBO n=95	RADIUM-223 n=210	PLACEBO n=107	RADIUM-223 n=196	PLACEBO n=99
Hematologic AEs								
Anemia	77 (13)	39 (13)	26 (13)	22 (23)	32 (15)	11 (10)	19 (10)	7 (7)
Neutropenia	13 (2)	2 (1)	5 (3)	0 (0)	3 (1)	1 (1)	5 (3)	1 (1)
Thrombocytopenia	38 (6)	6 (2)	16 (8)	3 (3)	15 (7)	3 (3)	8 (4)	0 (0)
Nonhematologic AEs								
Diarrhea	9 (2)	5 (2)	4 (2)	2 (2)	2 (1)	2 (2)	3 (2)	1 (1)
Nausea	10 (2)	5 (2)	5 (3)	3 (3)	3 (1)	0 (0)	2 (1)	2 (2)
Vomiting	10 (2)	7 (2)	5 (3)	5 (5)	3 (1)	1 (1)	2 (1)	1 (1)
Constipation	6 (1)	4 (1)	2 (1)	3 (3)	3 (1)	0 (0)	1 (1)	1 (1)

*Safety population included patients who received at least 1 dose; 1 patient in the placebo group received 1 injection of radium-223 (week 0) and is included in the radium-223 safety analysis.

Wiechno P, et al. ESMO 2013; Abs 2883

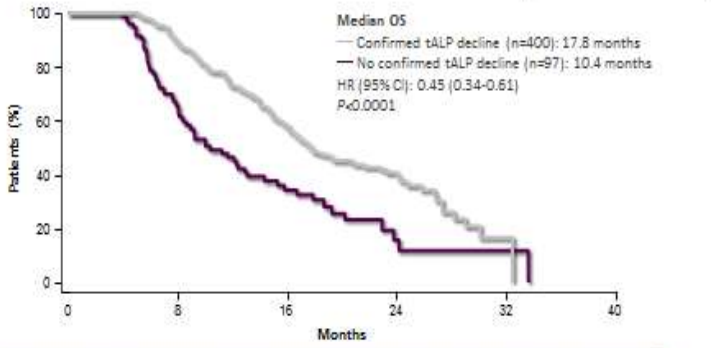
ALSYMPCA trial: Secondary endpoints

Time to SSE



BSoC, best standard of care; CI, confidence interval; HR, hazard ratio; SSE, symptomatic skeletal event.

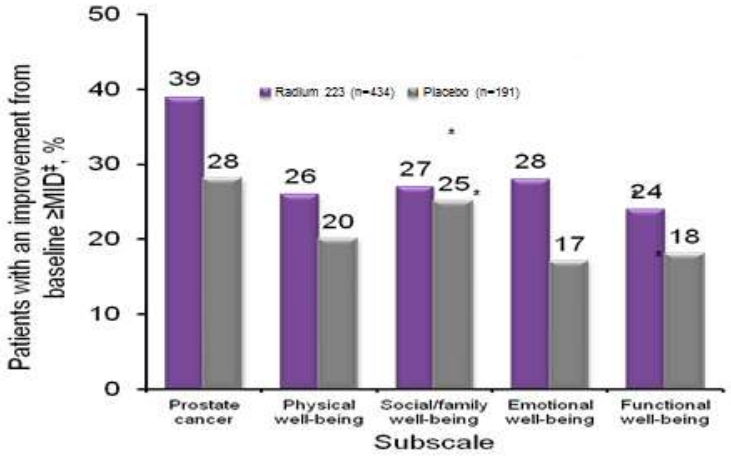
ALP and OS



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

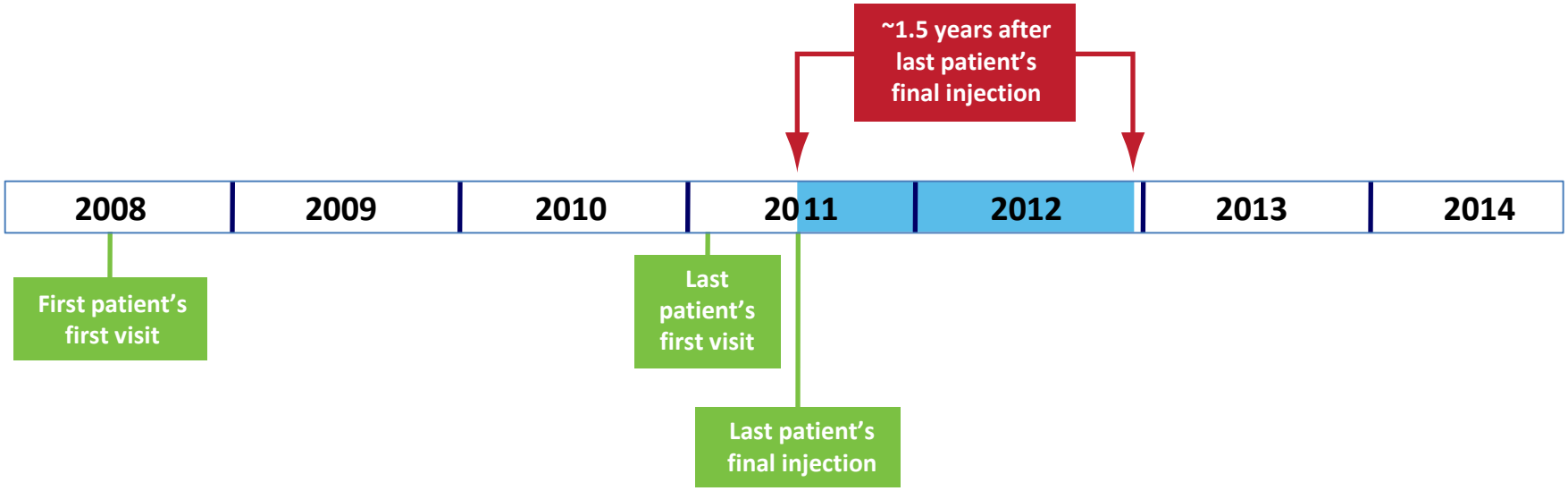
* Confirmed tALP decline was defined as any decrease from baseline at week 12, confirmed 28 weeks later

Quality of Life



Parker C, et al. *N Engl J Med.* 2013

ALSYMPCA Long-term Follow-Up



Of 921 patients randomized, 574 entered 3-year follow-up (radium-223, n = 406; placebo, n = 168)

Nilsson S, ASCO-GU 2014

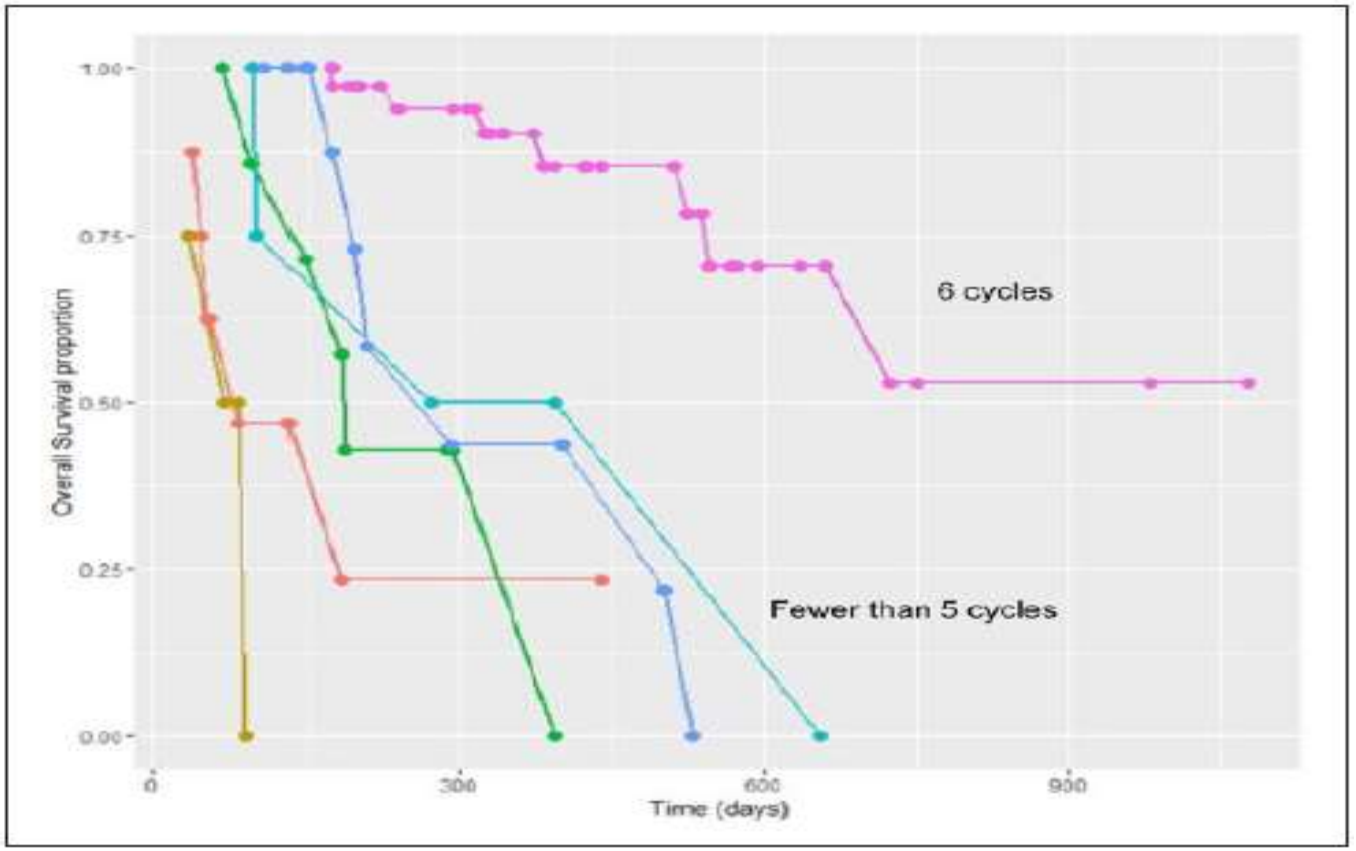
Treatment-Related Hematologic AEs

	Number (%) of Patients With Treatment-Related AEs					
	Radium-223 n = 404			Placebo n = 167		
Posttreatment Follow-Up AEs	All Grades	Grades 3/4	Grade 5	All Grades	Grades 3/4	Grade 5
Anemia	11 (3)	5 (1)	0	5 (3)	1 (1)	0
Aplastic anemia	1 (< 1)	1 (< 1)	0	0	0	0
Leukopenia	2 (< 1)	2 (< 1)	0	0	0	0
Neutropenia	2 (1)	2 (1)	0	0	0	0
Thrombocytopenia	4 (1)	0	0	0	0	0

Nonhematologic Treatment-Related AEs

	Number (%) of Patients With Treatment-Related AEs					
	Radium-223 n = 404			Placebo n = 167		
Posttreatment Follow-Up AEs	All Grades	Grades 3/4	Grade 5	All Grades	Grades 3/4	Grade 5
Cardiopulmonary failure	0	0	0	1 (1)	0	1 (1)
Nausea	0	0	0	1 (1)	0	0
Fatigue	0	0	0	1 (1)	0	0
General physical health deterioration	1 (< 1)	0	0	0	0	0
Multiorgan failure	1 (< 1)	0	1 (< 1)	0	0	0
Pneumonia	1 (< 1)	0	1 (< 1)	0	0	0
Weight decrease	1 (< 1)	0	0	0	0	0
Anorexia	1 (< 1)	0	0	0	0	0
Musculoskeletal pain	1 (< 1)	0	0	0	0	0
Pathologic fracture	2 (< 1)	1 (< 1)	0	0	0	0
Dizziness	1 (< 1)	0	0	0	0	0

^{223}Ra-chloride therapy in men with hormone-refractory prostate cancer and skeletal metastases: Real-world exprerience



Boni et al, Tumori J 2018

Sequencing Radium 223 (RA223) for metastatic castration-resistant prostate cancer (mCRPC) patients (pts) in the daily practice: preliminary results from a retrospective study in Italian Centers.

322

O. Caffo[1] – V. Frantellizzi[2] – L. Galli[3] – F. Monari[4] – G. Facchini[5] – S. Baldari[6] – M. Tucci[7] – F. Alongi[8] – R. Bortolus[9] – S. Agostini[10] – E. Biasco[3] – S. Fanti[11]
S. Rossetti[5] – S. Pignata[6] – C. Zichi[7] – M. Salgarello[12] – E. Borsatti[13] – E. Cortesi[2] – A. Sbrana[3] – G. Devincentis[2]
Santa Chiara Hosp (Trento): Depts of Medical Oncology[1] and Nuclear Medicine[10] – "Sapienza" University (Rome): Dept of Radiological, Oncological and Anatomo-Pathological Sciences[2] – AOU Pisana (Pisa): Medical Oncology Dept[3]
S. Orsola Malpighi Hosp (Bologna): Depts of Radiotherapy[4] and Nuclear Medicine[11] – INT Pascale (Naples): Dept of Uro-Gynaecological Oncology[5] – University of Messina (Messina): Dept of Biomedical and Dental Sciences and of Morphological and Functional Images[6] – San Luigi Gonzaga Hosp (Orbassano): Dept of Medical Oncology[7] – Sacro Cuore Don Calabria Cancer Care Center (Negrar): Depts of Radiation Oncology[8] and Nuclear Medicine[12]
NCI of Aviano (Aviano): Depts of Radiation Oncology[9] and Nuclear Medicine[13] - ITALY

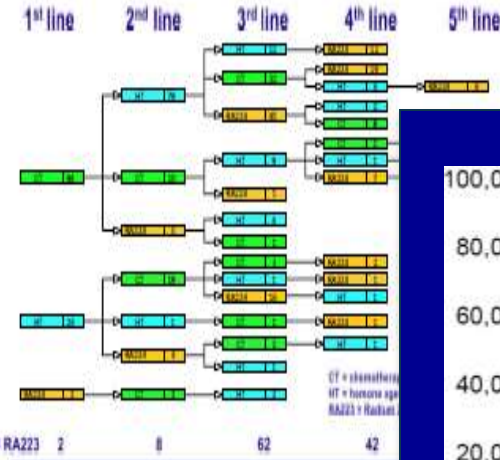
BACKGROUND

The potential advantage of the sequential use of the active drugs (ADs) able to prolong overall survival (OS) in mCRPC (abiraterone, cabazitaxel, docetaxel, enzalutamide, RA223) could be limited by the development of common mechanisms of resistance. According to its unique targeted alpha-radiation mechanism of action, it could be postulated that RA223 does not induce and is not affected by cross-resistance with other agents and consequently its incorporation in therapeutic sequences may improve clinical outcomes. The present study is aimed to describe the clinical outcomes of pts who received RA223 and at least two other ADs for mCRPC.

METHODS

We collected data of pts who received sequentially 3 or more ADs of which one was RA223. For each pt we recorded the clinical outcome of all treatments received for mCRPC. To assess the potential benefit from the RA223 addition in the therapeutic sequence we compared the cumulative survival from the start of the first line observed in this study to that observed in a contemporary series of 476 mCRPC pts sequentially treated with 3 or 4 ADs not comprising RA223 in Italian Hospitals (2017 ASCO Meeting Abs 5030). To make comparable the two series, we excluded from the analysis of no_RA223 series all pts with visceral mets.

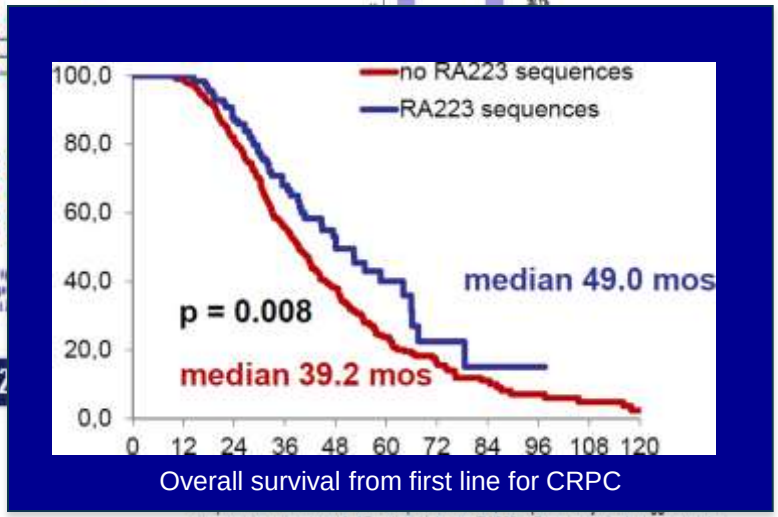
TREATMENTS SEQUENCES (with pts number)



Skeletal metastatic burden at RA2

< 3 bone mets	3.3%
3-10 bone mets	18.5%
> 10 bone mets	52.9%
superscan	21.0%
not reported	4.2%

RA223 full delivery (6 courses) rates



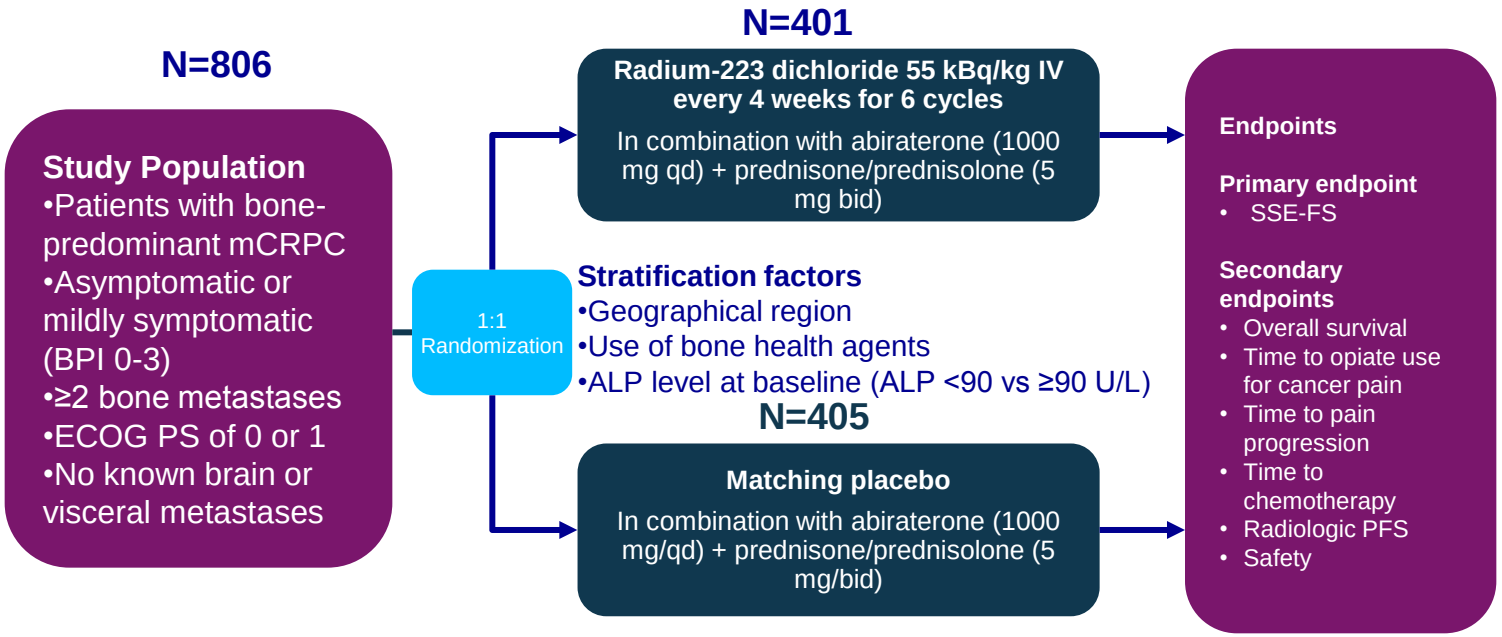
Overall survival from first line for CRPC

treatment sequencing of ADs that includes RA223 offers a survival advantage in mCRPC.

For further information please email to orazio.caffo@apss.tn.it

Caffo O. et al ASCO GU 2018 – poster # 322

ERA 223: phase III multinational, multicenter,randomized, double blind, placebo controlled, on Asymptomatic or Mildly Symptomatic CRPC with Bone Metastases with Radium-223 in Combination with Abiraterone and Prednisone



- ERA 223 was unblinded early on November 17, 2017, based on the recommendation of the IDMC

ClinicalTrials.gov. NCT02043678. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02043678. Accessed March 2018.

ERA trial [illegible] mmittee:

		erone plus nisone
Death, n. (%)		01 (27%)
Fractures (%)		24%

EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

30 November 2017
EMA/PRAC/790594/2017

Questions

The marketing authorisation holder (MAH) is requested to address the following questions:

Question 1. Please provide the marketing status and exposure to Ra223 dichloride in European Union (EU) Member States (MS), Iceland and Norway, and worldwide. This should include data from completed and ongoing studies and all post-marketing sources. Please provide any data, in addition to the REASSURE study[1], on extent of exposure to the Ra223 dichloride and abiraterone combination in post-marketing use.

Question 2. Provide an analysis of the complete dataset from the ERA 223 study[2] following the full survival sweep, and the reasons for the differences in outcome between the two arms (including type and localization of fractures as well as number, size and type of metastases). This should include all relevant safety endpoints, including mortality, fractures, the skeletal symptomatic events endpoint and its components. Please provide the causality assessment for all deaths. Available information regarding the Ra223 specific effects should be discussed.

Question 3. Please provide an analysis of the time to onset for fractures and death in the ERA 223 study. Discuss the timing of these events in the two study arms and any conclusion on the risk period. Provide an analysis of fractures depending on whether or not patients received bone modifying agents. Discuss potential mechanisms for the increased risk of fractures, including a possible pharmacodynamic interaction between Ra223 and abiraterone and prednisone/prednisolone.

Question 4. Provide Kaplan Meier curves for survival and fractures for all randomised controlled trials for Ra223 dichloride. An overview about data on combined endpoints and single separate endpoints, overall fractures, pathological and non-pathological fractures should also be presented and discussed.

Question 5. Please provide an overview of all clinical trials evaluating the radium Ra223 dichloride – abiraterone combination treatment, their current study status, populations involved and study questions addressed.

Question 6. Provide a comprehensive discussion of:

a) Possible reasons for the different results from the ERA 223 study and the pivotal phase III trial ALSYMPCA, including differences in disease (e.g. size and number of metastases), baseline characteristics, concomitant treatments and any other relevant factors, including differences between the two studies in exposure to Ra223 (i.e. number of injections administered).

b) Potential reasons for the conflicting data from the ERA 223 study and other studies and international early access programs.

c) The safety and efficacy of the combination of Ra223 dichloride and abiraterone with a particular focus on fractures and survival.

Question 7. Please discuss whether data on the combination of Ra223 dichloride and abiraterone from the ERA 223 study are relevant to the combination of Ra223 dichloride with other anti-androgens. Discuss relevant data from studies where some patients treated with Ra223 dichloride also received anti-androgens.

[1] Observational Study for the Evaluation of Long-term Safety of Radium-223 Used for the Treatment of Metastatic Castration Resistant Prostate Cancer (REASSURE)
[2] Study 15396 (ERA-223); NCT02043678; A phase III randomised, double-blind, placebo-controlled trial of radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naive subjects with bone predominant metastatic castration-resistant prostate cancer (CRPC)

EMA restricts use of prostate cancer medicine Xofigo

Press release

27/07/2018

EMA restricts use of prostate cancer medicine Xofigo

Medicine to be used only after two previous treatments or when other treatments cannot be taken

The European Medicines Agency (EMA) has concluded its review of the cancer medicine Xofigo (radium-223 dichloride), and has recommended restricting its use to patients who have had two previous treatments for metastatic prostate cancer (prostate cancer that has spread to the bone) or who cannot receive other treatments.

Xofigo must also not be used with the medicines Zytiga (abiraterone acetate) and the corticosteroid prednisone or prednisolone. Xofigo should not be used with other systemic cancer therapies, except for treatments to maintain reduced levels of male hormones (hormone therapy). The medicine should also not be used in patients who have no symptoms, in line with the current indication; in addition, the use of Xofigo is not recommended in patients with a low number of bone metastases called osteoblastic bone metastases.

Related information

- Xofigo: EPAR
- Xofigo: Article 20 procedures

Related content

- Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 23-26 July 2018 (27/07/2018)

Scheda AIFA

	Precedenti trattamenti per malattia resistente alla castrazione		
O	Precedente trattamento per malattia resistente alla castrazione	*Si*	
		No	
Se risposto NO,			
E	Il paziente può ricevere altri trattamenti?	*Si*	*blocca*
		No	
Se risposto Si, indicare i farmaci e l'approccio impiegato:			
O	Linee di terapia sistemiche già ricevute per malattia resistente alla castrazione	1	*blocca*
		2	
		3	
		≥4	
Per ciascuna linea di trattamento precedente indicare i farmaci ed il regime impiegato. Questa finestra e la successiva devono essere ripetute tante volte quante sono le N linee di terapia ricevute, indicando la N linea a cui ci si riferisce (1^, 2^, ecc.)			
E	Approcci terapeutici impiegati (possibili selezioni multiple)	Bicalutamide ad alte dosi	
		Switch da bicalutamide a flutamide	
		Switch da flutamide a bicalutamide	
		Sospensione di anti-androgeni	
		DES o altro estrogeno	
		Estramustina	
		Corticosteroidi	
		Docetaxel	
		Cabazitaxel	
		Mitoxantrone	
		Abiraterone	
		Enzalutamide	
		Sipuleucel-T	
		Radio-223 dicloruro	*blocca*
		Altro: specificare	

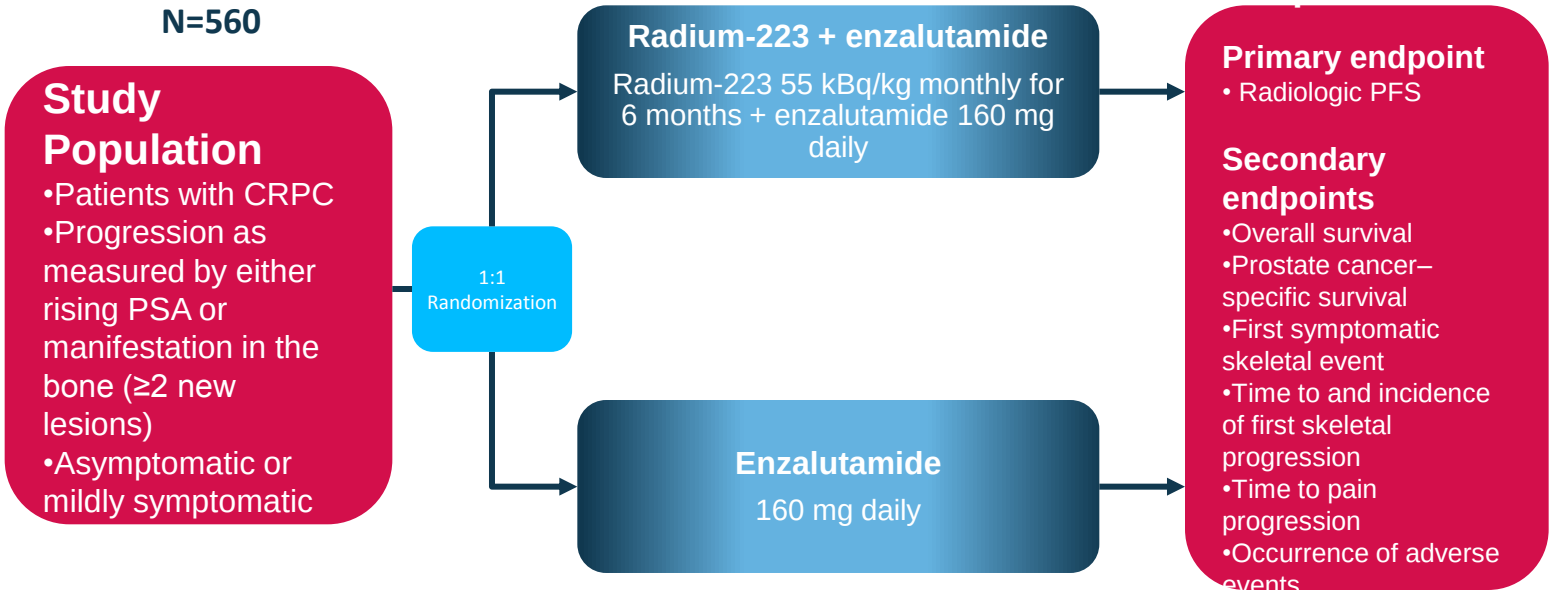
Scheda Aifa: eleggibilità

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)	

*ERA trial e Alsympca: TC e scintigrafia ossea

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

PEACE III: Concomitant Treatment of Asymptomatic or Mildly Symptomatic CRPC with Bone Metastases with Radium-223 in Combination with Enzalutamide

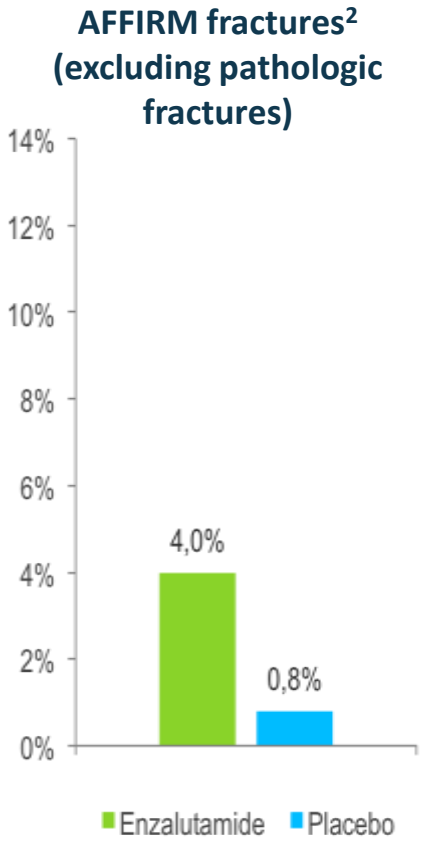


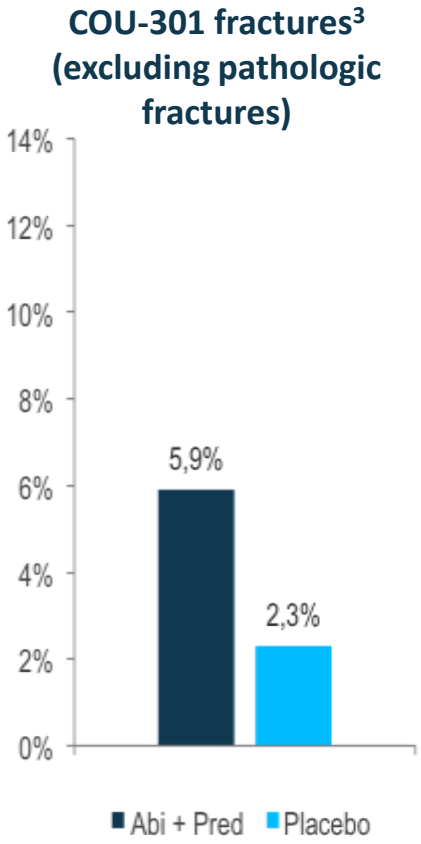
Emendamento post-ERA223: BHA a tutti i pazienti arruolati

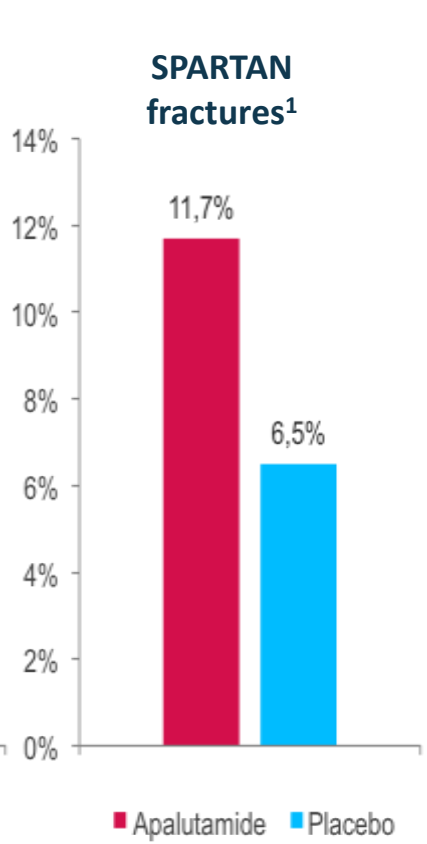
ECOG PS, Eastern Cooperative Oncology Group performance status; **IV**, intravenous; **CRPC**, castration-resistant prostate cancer; **PFS**, progression-free survival.

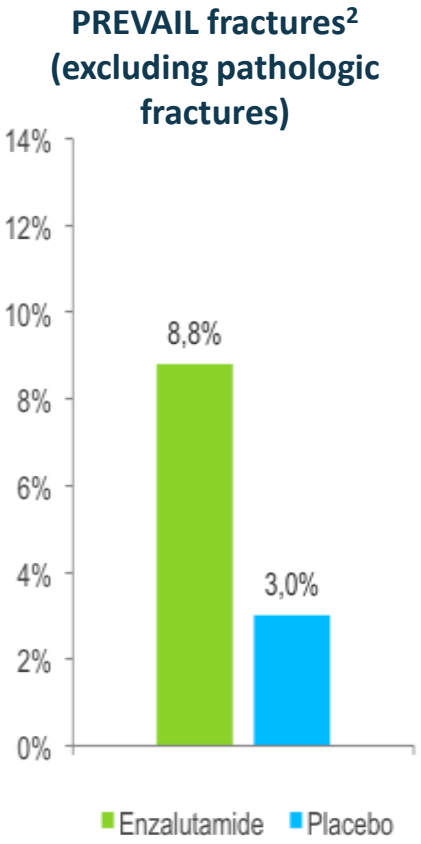
ClinicalTrials.gov. NCT02194842. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02194842. Accessed March 2018.

Apalutamide, Enzalutamide, Abiraterone + Prednisone: aumento del rischio di fratture non patologiche





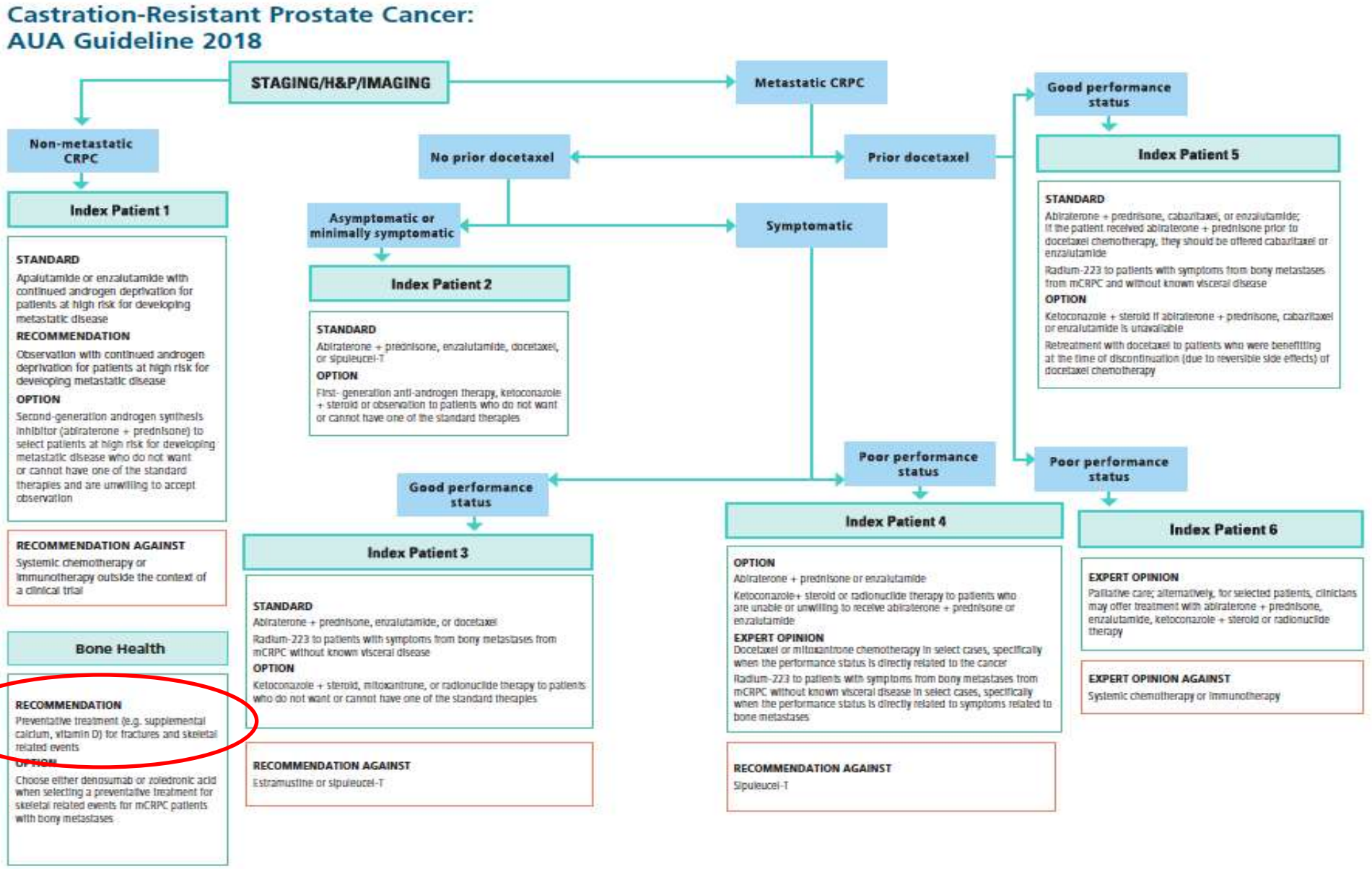




- The apalutamide USPI contains a warning and precaution to monitor and manage patients at risk of fractures according to treatment guidelines and consider the use of bone-targeted agents[4]
- In the PROSPER trial, 17% of enzalutamide-treated patients reported falls and fractures compared with 8% of placebo-treated patients[5]

USPI, U.S. prescribing information.
1. Smith MR *et al. N Engl J Med* 2018; doi:10.1056/NEJMoa1715546 [Epub ahead of print]. **2.** Xtandi (enzalutamide) [prescribing information]. Astellas Pharma US, Inc., Northbrook, IL. July 2017. **3.** Zytiga (abiraterone acetate) [prescribing information]. Janssen Biotech, Inc., Horsham, PA. February 2018. **4.** Erleada (apalutamide) [prescribing information]. Janssen Products, LP, Horsham, PA. February 2018. **5.** Hussain M *et al. N Engl J Med* 2018;378(26):2465–2474.

Bone Health


Castration-Resistant Prostate Cancer:
AUA Guideline 2018
STAGING/H&P/IMAGING
Non-metastatic CRPC
Index Patient 1
STANDARD
Apalutamide or enzalutamide with continued androgen deprivation for patients at high risk for developing metastatic disease
RECOMMENDATION
Observation with continued androgen deprivation for patients at high risk for developing metastatic disease
OPTION
Second-generation androgen synthesis inhibitor (abiraterone + prednisone) to select patients at high risk for developing metastatic disease who do not want or cannot have one of the standard therapies and are unwilling to accept observation
RECOMMENDATION AGAINST
Systemic chemotherapy or immunotherapy outside the context of a clinical trial
Bone Health
RECOMMENDATION
Preventative treatment (e.g. supplemental calcium, vitamin D) for fractures and skeletal related events
OPTION
Choose either denosumab or zoledronic acid when selecting a preventative treatment for skeletal related events for mCRPC patients with bony metastases
Metastatic CRPC
No prior docetaxel
Asymptomatic or minimally symptomatic
Index Patient 2
STANDARD
Abiraterone + prednisone, enzalutamide, docetaxel, or sipuleucel-T
OPTION
First- generation anti-androgen therapy, ketoconazole + steroid or observation to patients who do not want or cannot have one of the standard therapies
Good performance status
Index Patient 3
STANDARD
Abiraterone + prednisone, enzalutamide, or docetaxel
Radium-223 to patients with symptoms from bony metastases from mCRPC without known visceral disease
OPTION
Ketoconazole + steroid, mitoxantrone, or radionuclide therapy to patients who do not want or cannot have one of the standard therapies
RECOMMENDATION AGAINST
Estramustine or sipuleucel-T
Prior docetaxel
Symptomatic
Poor performance status
Index Patient 4
OPTION
Abiraterone + prednisone or enzalutamide
Ketoconazole+ steroid or radionuclide therapy to patients who are unable or unwilling to receive abiraterone + prednisone or enzalutamide
EXPERT OPINION
Docetaxel or mitoxantrone chemotherapy in select cases, specifically when the performance status is directly related to the cancer
Radium-223 to patients with symptoms from bony metastases from mCRPC without known visceral disease in select cases, specifically when the performance status is directly related to symptoms related to bone metastases
RECOMMENDATION AGAINST
Sipuleucel-T
Good performance status
Index Patient 5
STANDARD
Abiraterone + prednisone, cabazitaxel, or enzalutamide; If the patient received abiraterone + prednisone prior to docetaxel chemotherapy, they should be offered cabazitaxel or enzalutamide
Radium-223 to patients with symptoms from bony metastases from mCRPC and without known visceral disease
OPTION
Ketoconazole + steroid if abiraterone + prednisone, cabazitaxel or enzalutamide is unavailable
Retreatment with docetaxel to patients who were benefitting at the time of discontinuation (due to reversible side effects) of docetaxel chemotherapy
Poor performance status
Index Patient 6
EXPERT OPINION
Palliative care; alternatively, for selected patients, clinicians may offer treatment with abiraterone + prednisone, enzalutamide, ketoconazole + steroid or radionuclide therapy
EXPERT OPINION AGAINST
Systemic chemotherapy or immunotherapy

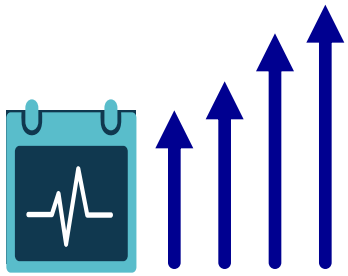
ESMO guidelines W[illegible]oup Bone health in cancer patient[illegible] practice guidelines

Coleman R, Ann Oncol 2014

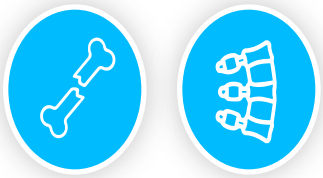
ALSYMPCA: vantaggio significativo in OS, SSE e Quality of Life

ALSYMPCA (Phase III, randomized, double-blind) assessed the efficacy and safety of radium-223 in combination with BSOC in men with mCRPC

A total of **901 patients** were randomized

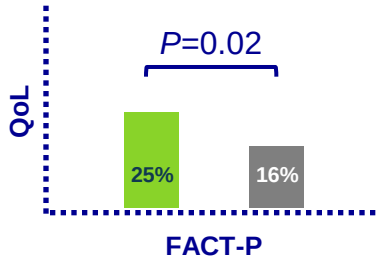


Radium-223 significantly improved OS of patients, with a **30% reduction in risk of death** compared with placebo (14.9 months vs 11.3 months, HR: 0.70; 95% CI: 0.58–0.83; *P*<0.001)



Radium-223 treatment **increased the time to first SSE** compared with placebo (15.6 months vs 9.8 months, HR: 0.66; 95% CI: 0.52–0.83)

Patients in the radium-223 group experienced **fewer Grade 3 or 4 AEs** (56% vs 62%), **serious AEs** (47% vs 60%), **and discontinuations due to AEs** (16% vs 21%) compared with the placebo group



Radium-223 **significantly improved QoL based on FACT-P** (25% of radium-223 patients vs 16% of placebo patients, *P*=0.02)

AE, adverse event; **BSOC**, best standard of care; **CI**, confidence interval; **HR**, hazard ratio; **mCRPC**, metastatic castration-resistant prostate cancer; **OS**, overall survival; **QoL**, quality of life; **SSE**, symptomatic skeletal event.

Parker C *et al. N Engl J Med* 2013;369:213–223.

roberto.sabbatini@unimore.it