Rádio-223 como opção terapêutica no mCRPC

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Declaração sobre Conflito de Interesses

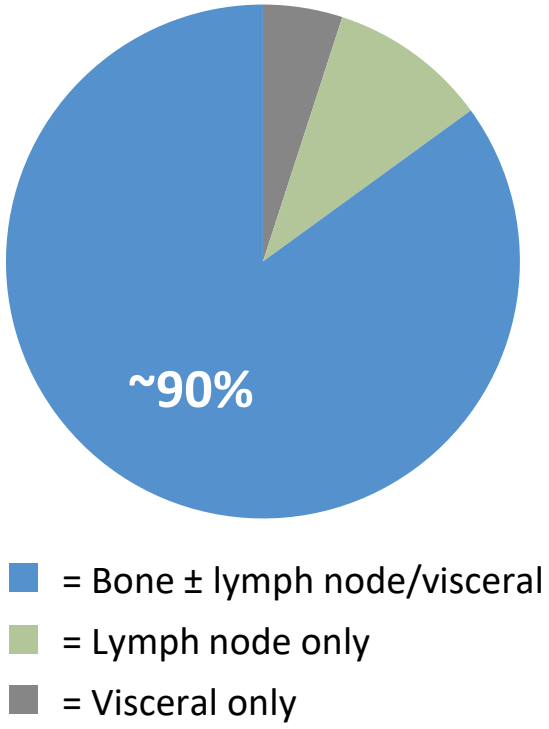
De acordo com a Resolução 1595 / 2000 do Conselho Federal de Medicina e com a RDC 96 / 2008 da ANVISA, declaro que:

- ***Pesquisa Clínica*: como médico investigador, participo de estudos patrocinados por: Roche, BMS, Janssen, Astra Zeneca**
- ***Apresentações*: como palestrante convidado, participei de eventos: Janssen, Sanofi, GSK, Bayer, Astellas, BMS, MSD**
- ***Advisory Board*: Bayer, Astellas, Janssen, MSD, BMS**

Não possuo ações de quaisquer destas companhias farmacêuticas.

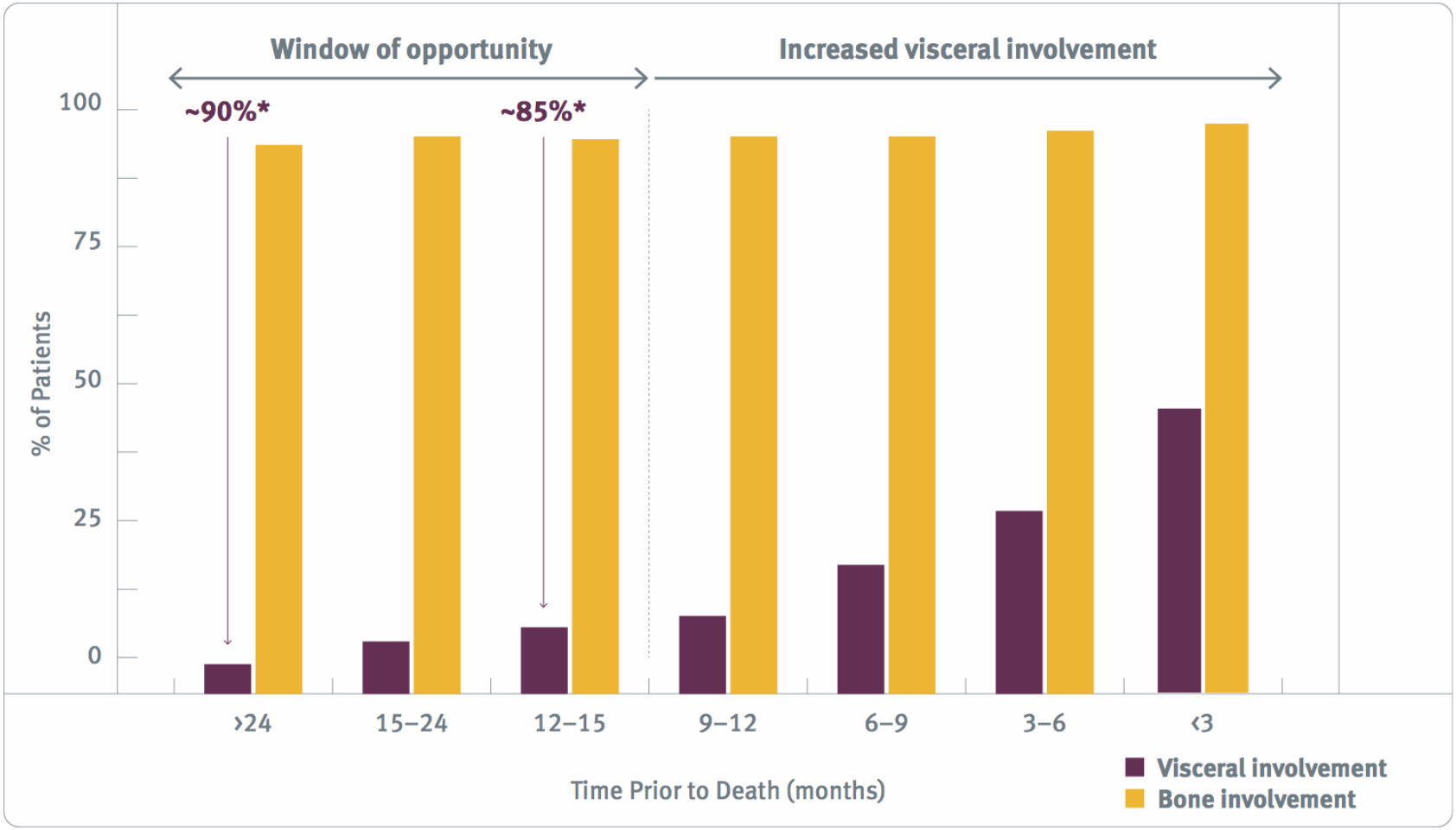
Bone is the most common site of metastases in prostate cancer[1–3]

- >90% of patients with mCRPC have radiologic evidence of bone metastases[1]
- Death from prostate cancer is often due to bone disease and its complications[2]
- The number of bone metastases detected by bone scan is an important indicator of prognosis and overall survival in patients with prostate cancer[3]
- The bone-targeted therapies bisphosphonates and denosumab have not shown improved survival
  - Derived benefits are primarily limited to pain relief and delay of skeletal events[4–13]



1. Tannock et al. N Engl J Med. 2004;351:1502–1512; 2. Lange and Vessella. Cancer Metastases Rev. 1998–1999;17:331–336; 3. Halabi et al. J Clin Oncol. 2016;34:1652–1659; 4. Lipton. Semin Oncol. 2010;37:S15–S29; 5. Adami. Cancer. 1997;80:1674–1679; 6. Silberstein. Semin Radiat Oncol. 2000;10:240–249; 7. Fizazi et al. J Clin Oncol. 2009;27:1564–1571; 8. Fizazi et al. Lancet. 2011;377:813–822; 9. Finlay et al. Lancet Oncol. 2005;6:392–400; 10. Lewington. J Nucl Med. 2005;46(suppl):38S–47S; 11. Sartor. Asian J Androl. 2011;13:366–368; 12. Sartor and Bruland. Clin Genitourin Cancer. 2011;9:1–2; 13. Sartor et al. Asian J Androl. 2011;13:783–784.

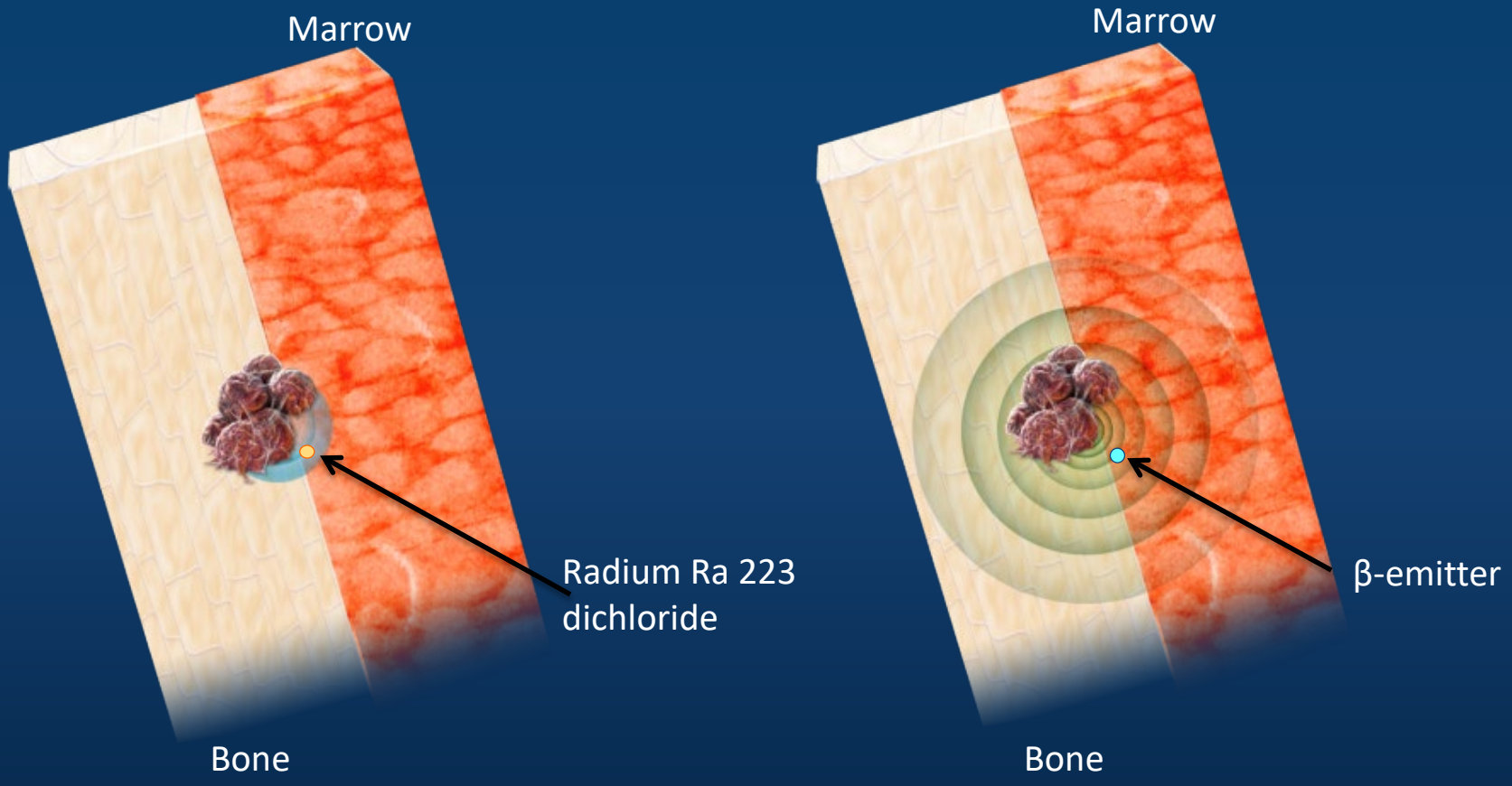
Development of visceral metastatic disease in late stages



* Patients that have metastasis only in the bone.

eference: Pezaro CJ, et al. Eur Urol. 2014;65:270–273.

Short Range of α-Emitters Reduces Bone Marrow Exposure[1]



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

Range of β-particle:
(long range – 10 to 1000 cell diameters[2])

SOURCE: 1. Henriksen G, et al. *Cancer Res.* 2002;62:3120–3125. **2.** Brechbiel MW. *Dalton Trans.* 2007;43:4918–4928.

ALSYMPCA: Study Design

PATIENTS (N=921)
- Confirmed symptomatic CRPC
- ≥2 bone metastases
- No known visceral metastases
- Post-docetaxel, unfit for docetaxel, or refused docetaxel[a]

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

Radium-223 (50 kBq/kg IV) 6 injections at 4-week intervals + best standard of care[b]

Placebo (saline) 6 injections at 4-week intervals + best standard of care[b]

- 136 centers in 19 countries
- Planned follow-up is 3 years

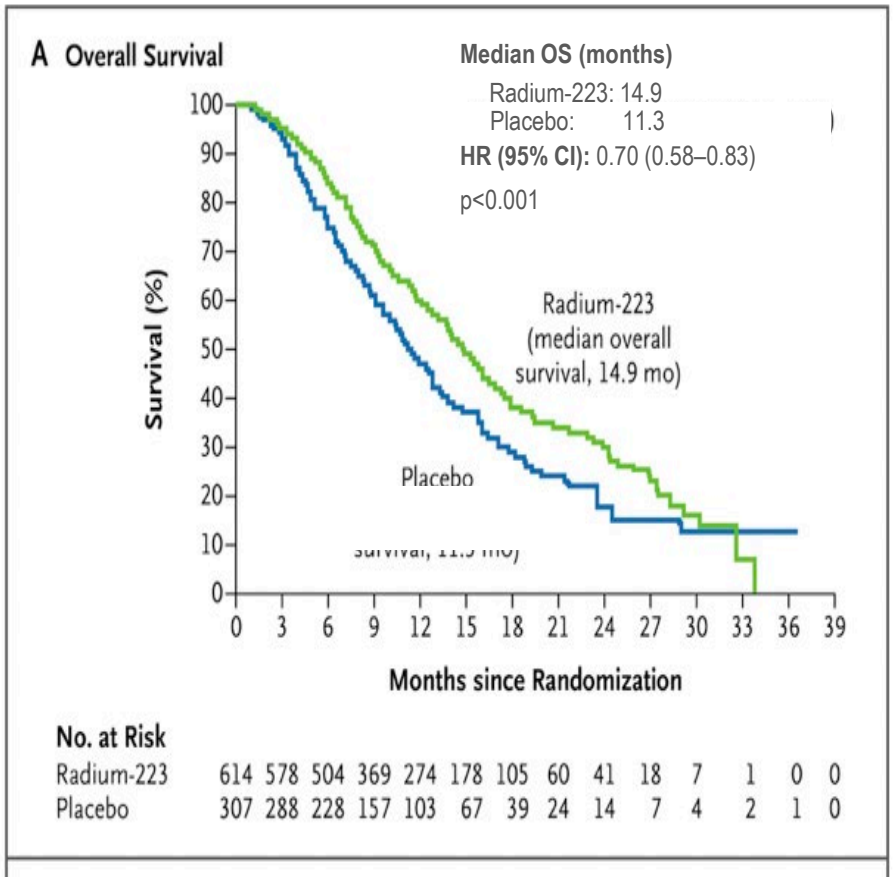
ALSYMPCA was halted early after the positive efficacy results reported from a planned interim analysis of 809 patients with 314 deaths occurred. An updated analysis of efficacy and safety was performed from all 921 enrolled patients when 528 deaths had occurred.

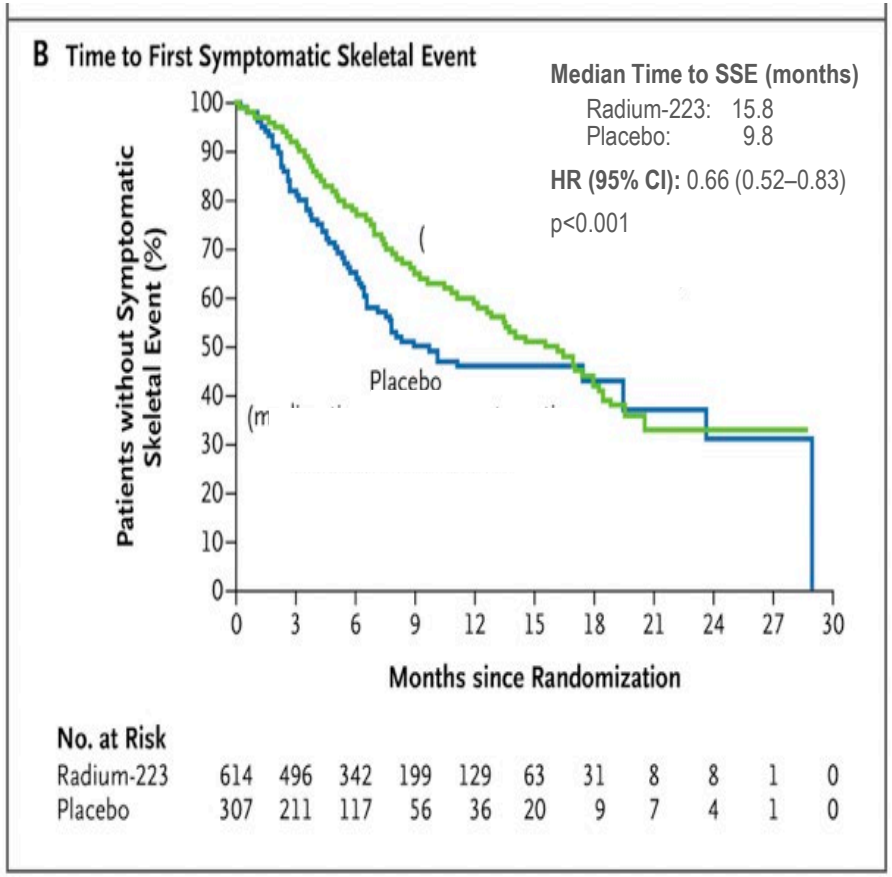
ALP, alkaline phosphatase; ALSYMPCA, ALpharadin in SYMptomatic Prostate CAncer; CRPC, castration-resistant prostate cancer.

a. Unfit for docetaxel includes patients who were ineligible for docetaxel, refused docetaxel, or lived where docetaxel was unavailable.
b. Best standard of care defined as a routine standard of care at each center, e.g., local external beam radiation therapy, corticosteroids, antiandrogens, estrogens (e.g., stilbestrol), estramustine, or ketoconazole.

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

ALSYMPCA
BSC + Radium-223 vs BSC + Placebo in mCRPC



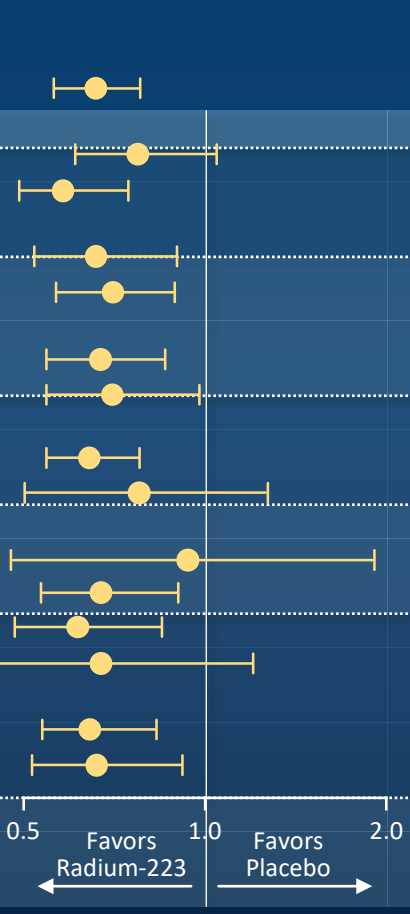


BSC, best standard-of-care; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; SSE, symptomatic skeletal event

Parker C, et al. N Engl J Med. 2013;369:213–23.

ALSYMPCA Updated Analysis: Radium-223 Improved OS Across All Patient Subgroups

SUBGROUP	PATIENTS (n) RADIUM-223	PATIENTS (n) PLACEBO	MEDIAN OS (months) RADIUM-223	MEDIAN OS (months) PLACEBO	HR	95% CI
All patients	614	307	14.9	11.3	0.70	0.58-0.83
Total ALP						
<220 U/L	348	169	17.0	15.8	0.82	0.64-1.07
≥220 U/L	266	138	11.4	8.1	0.62	0.49-0.79
Current use of bisphosphonates						
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
Prior use of docetaxel						
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 PS						
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[a]	345	168	13.9	10.4	0.68	0.54-0.86
No[b]	269	139	16.4	12.8	0.70	0.52-0.93



ALP, alkaline phosphatase; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio.

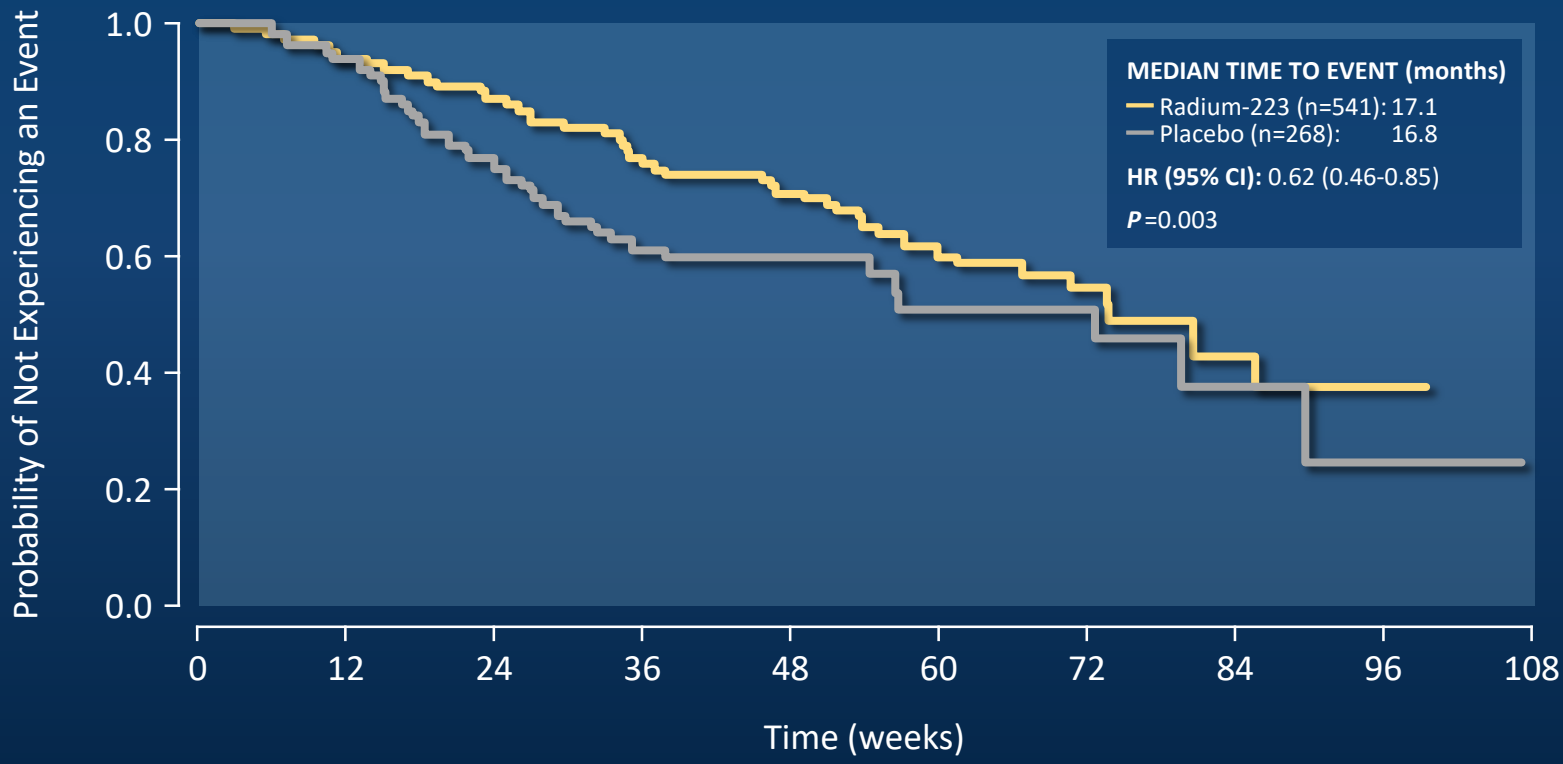
a. Includes patients with a score of 2 or 3 on the World Health Organization (WHO) ladder for cancer pain.

b. Includes patients without pain or opioid use at baseline and patients with a score of 1 on the WHO ladder for cancer pain.

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

Radium-223 Delays Time to Marked Deterioration of ECOG PS (≥2 Points)

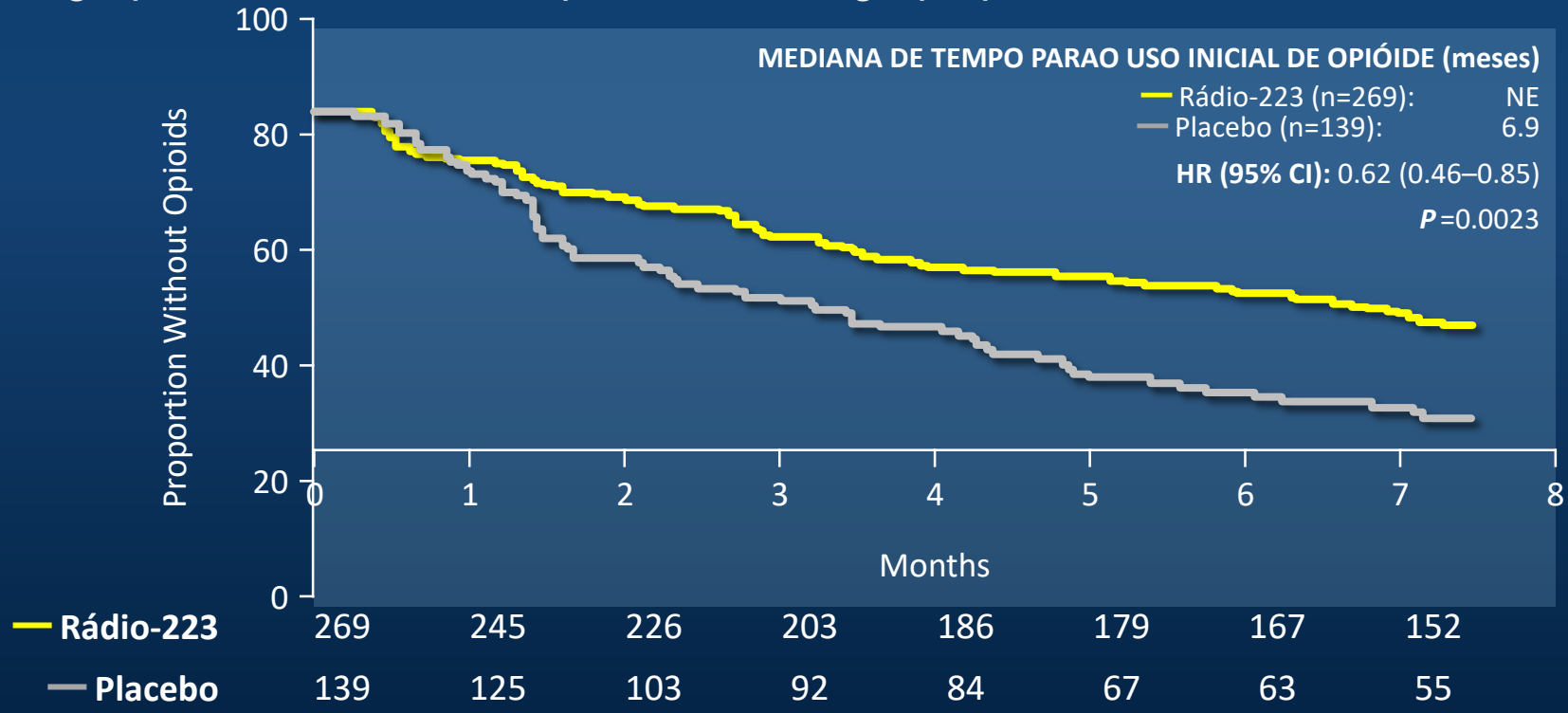
Time to ECOG PS deterioration (≥2 points) was significantly delayed in the radium-223 group compared with the placebo group.



SOURCE: Sartor AO, et al. *J Clin Oncol*. 30, 2012 (suppl; abstr 4551).

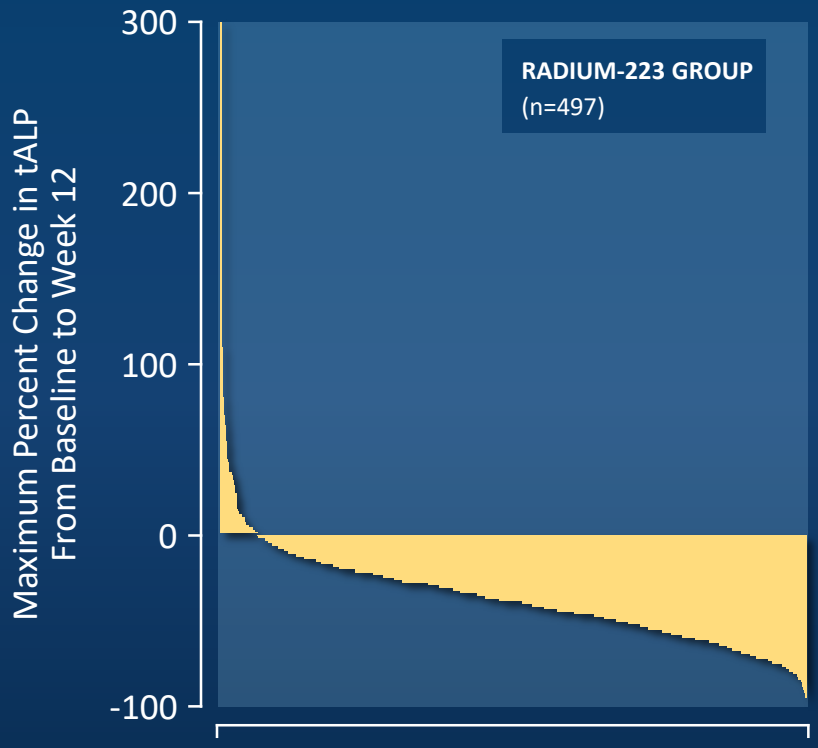
Tempo para o início do uso de Opióide foi significativamente mais longo com Rádio-223

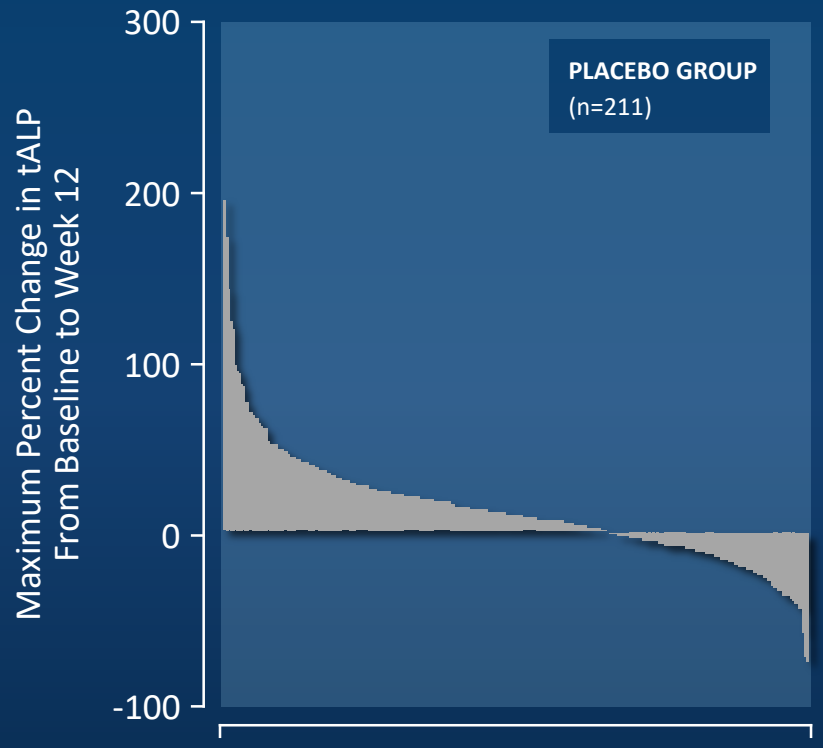
- 269/614 (44%) de pacientes no grupo do rádio-223 e 139/307 (45%) pacientes no grupo placebo não utilizavam opióide basal
- Destes, 96 (36%) pacientes do grupo do rádio-223 versus 70 (50%) pacientes do grupo placebo necessitatam de uso de opióide para alívio de dor
- Mediana de tempo para o uso inicial de opióide foi significativamente mais longo no grupo do rádio-223, comparado com o grupo placebo



SOURCE: Nilsson S, et al. *J Clin Oncol.* 31, 2013 (suppl; abstr 5038).

Waterfall Plot of Maximum Percent Change in tALP From Baseline to Week 12





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

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.

NUMBER OF PATIENTS WITH AEs OCCURRING IN ≥5% OF PATIENTS IN EITHER TREATMENT GROUP

	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

AE, adverse event.

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

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

Low Incidence of Grade 3 or 4 Hematologic AEs, Regardless of Prior Docetaxel Use

- Overall, there was a low incidence of myelosuppression in the docetaxel subgroups
  - The total incidence of grade 3 or 4 thrombocytopenia was significantly higher in patients with prior versus no prior docetaxel use (7% vs 2%, respectively; *P*=0.001)
  - Patients with a history of prior docetaxel had a significantly higher incidence of grade 3 or 4 thrombocytopenia with radium-223 versus placebo (9% vs 3%, respectively; *P*=0.01)
- No statistically significant difference was seen in incidence of anemia or neutropenia between docetaxel subgroups, or between radium-223 and placebo within each docetaxel subgroup

	NO PRIOR DOCETAXEL			PRIOR DOCETAXEL			TOTAL		
PATIENTS WITH GRADE 3 or 4 AEs, n (%)	**RADIUM-223** (n=253)	**PLACEBO** (n=130)	***P* VALUE***	**RADIUM-223** (n=347)	**PLACEBO** (n=171)	***P* VALUE***	**NO PRIOR DTX** (n=383)	**PRIOR DTX** (n=518)	***P* VALUE***
Anemia	27 (11)	15 (12)	NS	50 (14)	24 (14)	NS	42 (11)	74 (14)	NS
Neutropenia	2 (1)	1 (1)	NS	11 (3)	1 (1)	NS	3 (1)	12 (2)	NS
Thrombocytopenia	7 (3)	1 (1)	NS	31 (9)	5 (3)	0.01	8 (2)	36 (7)	0.001

AEs, adverse events; DTX, docetaxel; NS, not statistically significant.

**P* values are based on Fisher's exact test; not corrected for multiple testing.

SOURCE: Vogelzang NJ, et al. *J Clin Oncol.* 31, 2013 (suppl; abstr 5068).

Hematologic Values Were Similar for Radium-223 and Placebo in Patients Receiving Post-Study Chemotherapy

For patients who received chemotherapy after the last dose of study drug (n=147), median values of hemoglobin, neutrophils, and platelets were similar for the radium-223 and placebo groups from baseline to month 12.

	HEMOGLOBIN, g/dL				NEUTROPHILS (ABSOLUTE) × 10⁹/L				PLATELETS × 10⁹/L			
	RADIUM-223 (n=93)		PLACEBO (n=54)		RADIUM-223 (n=93)		PLACEBO (n=54)		RADIUM-223 (n=93)		PLACEBO (n=54)	
	n	MEDIAN (MIN-MAX)	n	MEDIAN (MIN-MAX)	n	MEDIAN (MIN-MAX)	n	MEDIAN (MIN-MAX)	n	MEDIAN (MIN-MAX)	n	MEDIAN (MIN-MAX)
Baseline*	93	11.2 (7.7-14.6)	54	11.4 (7.7-15.1)	91	3.6 (0.9-26.0)	49	4.6 (1.9-16.4)	93	214 (67-484)	54	241 (80-563)
Month 2	51	10.6 (6.6-14.2)	34	10.8 (7.7-14.2)	47	4.4 (0.5-24.4)	30	5.7 (1.6-13.1)	51	197 (48-427)	34	256 (87-385)
Month 4	42	11.0 (6.4-13.6)	20	10.6 (7.1-14.6)	42	3.9 (1.3-10.8)	19	4.6 (1.1-8.9)	42	241 (48-437)	20	221 (131-411)
Month 6	24	11.1 (8.6-12.4)	14	11.1 (8.6-14.0)	23	3.5 (0.5-6.3)	12	4.7 (1.5-12.2)	24	216 (85-423)	14	217 (99-305)
Month 8	13	10.5 (8.2-12.5)	7	10.8 (10.3-12.8)	12	3.5 (1.9-9.4)	7	3.9 (3.0-6.4)	13	202 (26-512)	7	288 (168-565)
Month 10	14	10.2 (7.9-13.1)	9	11.8 (9.9-13.3)	13	3.6 (1.1-8.9)	8	4.6 (3.0-8.5)	14	255 (95-370)	9	259 (179-512)
Month 12	8	10.5 (9.0-13.2)	6	10.7 (9.8-13.4)	8	5.0 (2.5-7.1)	6	5.6 (2.8-8.9)	8	305 (164-464)	6	264 (89-394)

*Lab. value before start of chemotherapy (after end of study treatment).

SOURCE: Sartor O, et al. *Ann Oncol.* 2012 (suppl; abstr 936P).

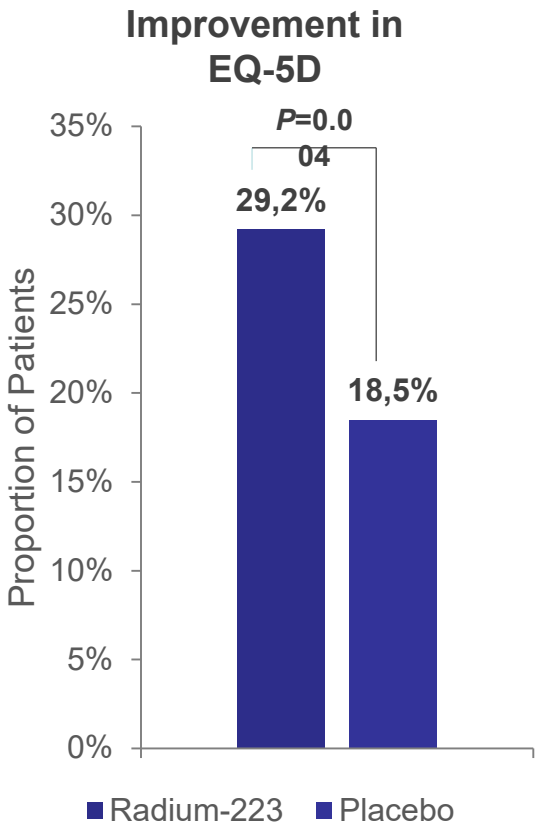
Safety: Treatment-Related Adverse Events Reported During 3-Year Follow-up

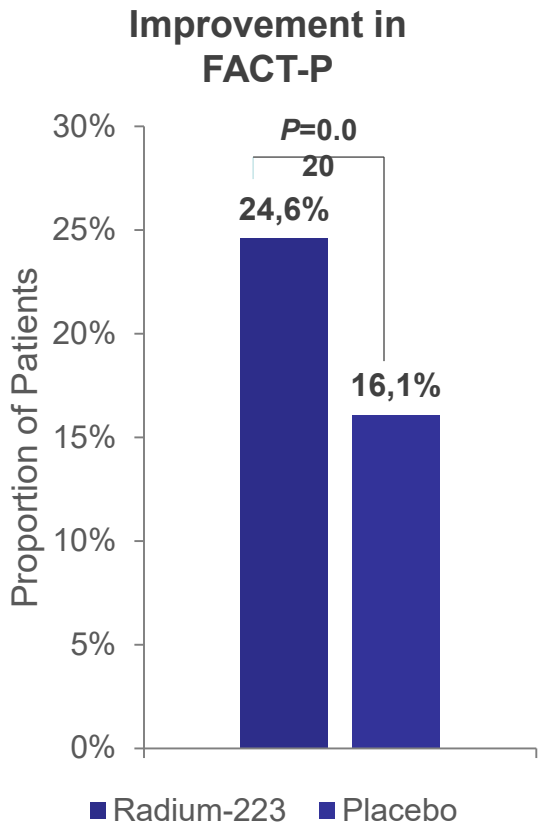
	RADIUM-223 (n=404)*			PLACEBO (n=167)*		
POSTTREATMENT FOLLOW-UP AEs	ALL GRADES, n (%)	GRADE 3/4, n (%)	GRADE 5, n (%)	ALL GRADES, n (%)	GRADE 3/4, n (%)	GRADE 5, n (%)
Hematologic AEs						
Anemia	11 (3)	5 (1)	0	5 (3)	1 (1)	0
Aplastic anemia	1 (<1)	1 (<1)	0	0	0	0
Leukopenia	2 (<1)	2 (<1)	0	0	0	0
Neutropenia	2 (<1)	2 (<1)	0	0	0	0
Thrombocytopenia	4 (1)	0	0	0	0	0
Nonhematologic AEs						
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

*Safety population for patients entering 3-year follow-up.

Nilsson S, et al. *Eur Urol.* 2013;(Suppl 12):123–180. Abstract P124.

Improved Overall Survival with Radium-223 Was Accompanied by Superior Quality of Life Outcomes





CI, confidence interval; **EBRT**, external beam radiation therapy; **HR**, hazard ratio; **mCRPC**, metastatic castration-resistant prostate cancer; **SSE**, symptomatic skeletal event

Nilsson S *et al. Ann Oncol* 2016;27:868–874.

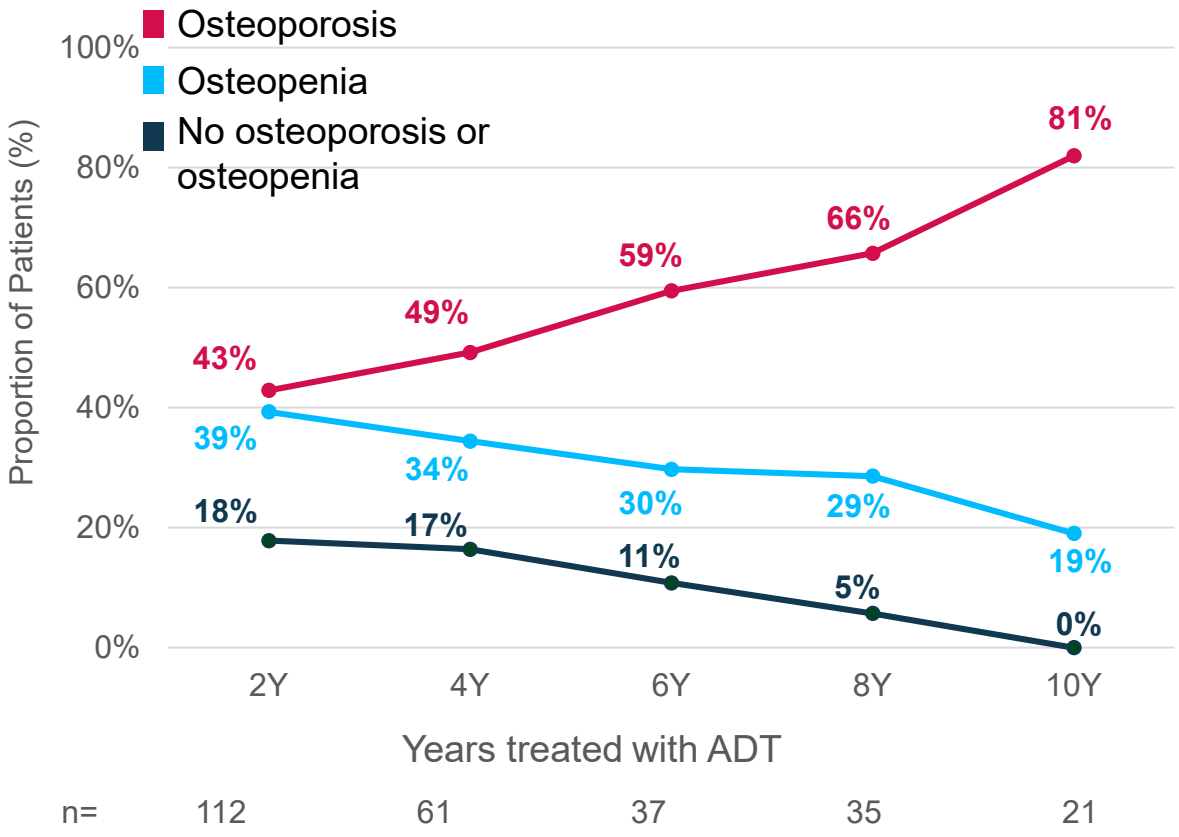
Prostate Cancer Patients are at an Elevated Risk of Osteoporosis Due to Standard Androgen Deprivation Therapy

LACOG
LATIN AMERICAN COOPERATIVE ONCOLOGY GROUP

1

- Prevalence of osteoporosis or osteopenia in ADT-treated prostate cancers is high, with up to 85% of patients experiencing poor bone health[1]
- The median survival time of men with non-metastatic prostate cancer treated with ADT is greater than 7 years[3]

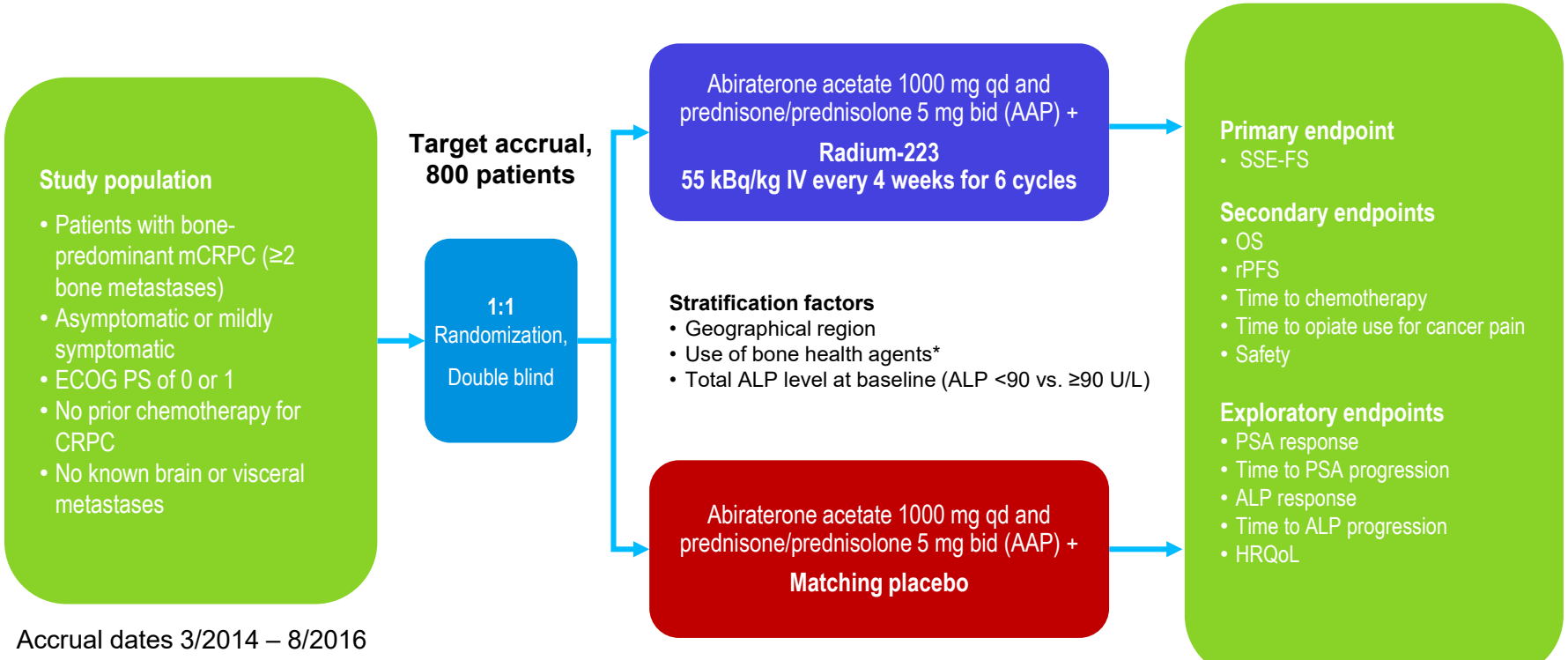
The rate of osteoporosis in men treated with ADT increases over time[4,5]



ADT, androgen deprivation therapy; **CI**, confidence interval; **GnRH**, gonadotropin-releasing hormone; **HR**, hazard ratio; **NAH**, novel anti-hormonal, **PCa**, prostate cancer.

1. Cianferotti L *et al. Oncotarget* 2017;8:75646–75663. **2.** Rachner TD et *al. Lancet Diabetes Endocrinol* 2018; doi:10.1016/S2213-8587(18)30047-0 [Epub ahead of print].
3. Saad F *et al. J Clin Oncol* 2008;26:5465–5476. **4.** Taylor LG *et al. N Engl J Med* 2009;115:2388–2399. **5.** Morote J *et al. Urology* 2007;69:500–504.

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 study was 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.

Smith M *et al.* Presented at European Society for Medical Oncology; Munich, Germany; October 19–23, 2018.

Características basais (ITT)

- 806 patients enrolled between 30 March 2014 and 12 August 2016

Characteristic	AAP + radium-223 N=401	AAP + placebo N=405
Age, median (IQR), years	71 (65–77)	71 (66–77)
White race, n (%)	285 (71)	284 (70)
Gleason score ≥8 at diagnosis, n (%)	246 (61)	233 (58)
>5 bone metastases or superscan, n (%)	265 (66)	264 (65)
Concurrent use of denosumab or bisphosphonates, n (%)	157 (39)	172 (42)
Medical history of osteoporosis, n (%)	21 (5)	9 (2)
BPI-SF Worst Pain Score 0 (asymptomatic), n (%)	195 (49)	198 (49)
Laboratory values, median (IQR)		
PSA (µg/L)	30 (12–92)	31 (11–77)
ALP (U/L)	129 (82–251)	121 (84–214)
LDH (U/L)	224 (185–370)	218 (180–32)
Prior enzalutamide	32 (8)	21 (5)

AAP, abiraterone acetate and prednisone/prednisolone; ALP, alkaline phosphatase; BPI-SF, brief pain inventory short form; IQR, interquartile range; ITT, intention-to-treat; LDH, lactate dehydrogenase; PSA, prostate-specific antigen.
Smith M *et al.* Presented at European Society for Medical Oncology; Munich, Germany; October 19–23, 2018.

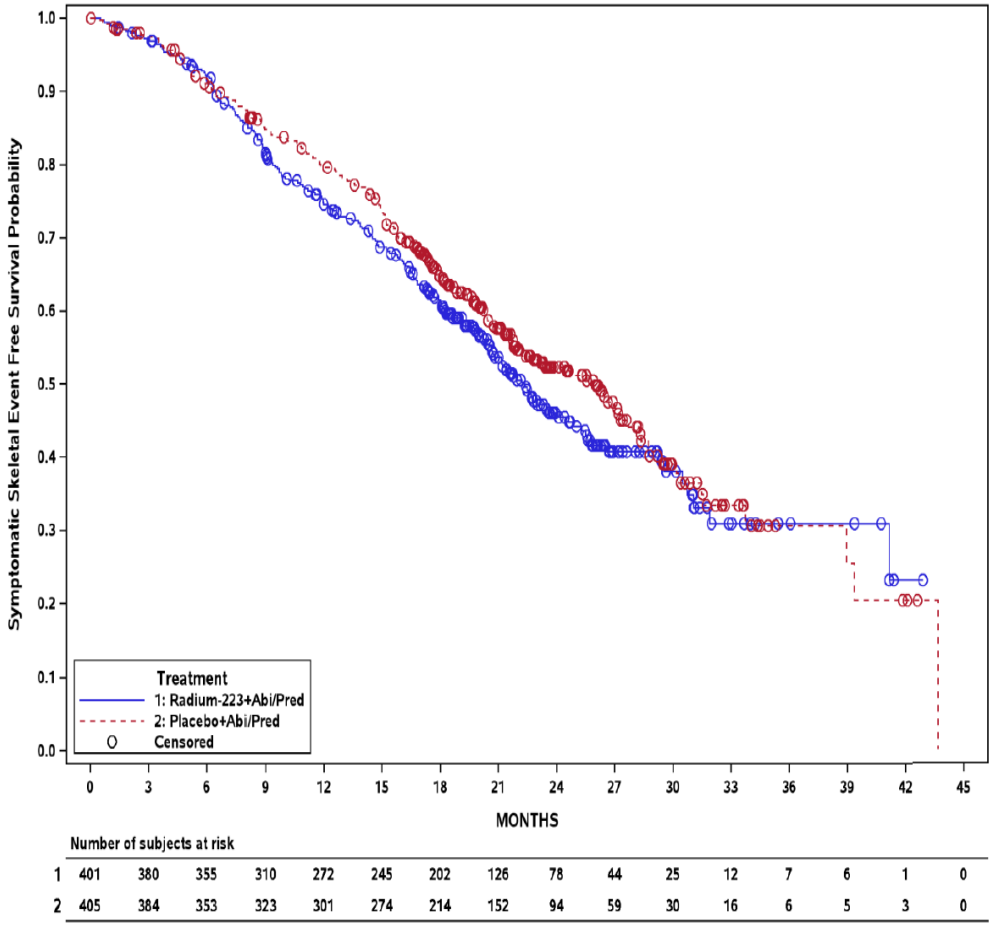
Quebra do cego (IDMC) Nov. 2017

- The study was fully accrued and all patients had completed either radium-223 or placebo by Feb 2017.
- IDMC met in Nov 2017 and noted more fractures and deaths in the AAP + radium-223 arm than in the AAP arm
- Unblinding was recommended
- All study procedures and treatment continued per protocol after unblinding.
- Protocol amended to allow initiation of BHA

Data at time of IDMC meeting		
	AAP+ Radium 223	AAP+ Placebo
Deaths (safety analysis set)	34.7% (136/392)	28.2% (111/394)
Overall survival (ITT) HR (95% CIs), 2-sided P value	1.347 (1.047, 1.732) 0.02	
Median overall survival (95% CIs) (months)	30.7 (25.2, 35.6)	33.3 (30.2, A)
≥1 fracture	26.0% (102/392)	8.1% (32/394)

Smith M et al. Presented at European Society for Medical Oncology; Munich, Germany; October 19–23, 2018.

Análise primária planejada – Jun. 2018
Sobrevida livre de SSE (ITT)



SSE-FS	AAP + radium-223 N=401	AAP + placebo N=405
Events, n (%)	196 (49)	190 (47)
Median (95% CI), months	22.3 (20.4–24.8)	26.0 (21.8–28.3)
HR (95% CI)	1.122 (0.917−1.374)	
P-value (2-sided)	0.2636	

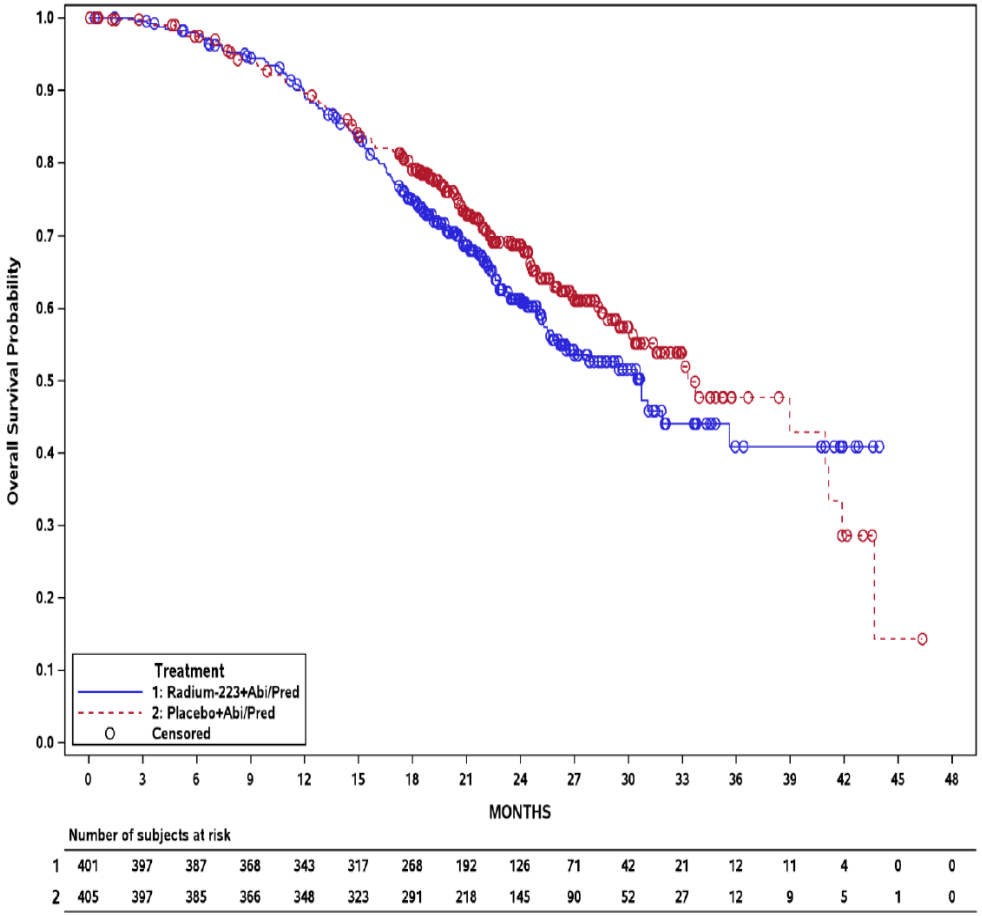
AAP, abiraterone acetate and prednisone/prednisolone; ITT, intention-to-treat; SSE-FS, symptomatic skeletal event-free survival.
Smith M *et al.* Presented at European Society for Medical Oncology; Munich, Germany; October 19–23, 2018.

Tipos de SSEs (ITT)

	AAP + radium-223 N=401	AAP + placebo N=405
Patients with ≥1 SSE or death, n (%)	196 (49)	190 (47)
First event of EBRT*	73 (37)	80 (42)
First event of symptomatic pathological bone fracture*	35 (18)	17 (9)
First event of spinal cord compression*	10 (5)	19 (10)
First event of tumour-related orthopaedic surgical intervention*	4 (2)	1 (0.5)
Death*,†	74 (38)	73 (38)

*Denominator is the total number of patients with ≥1 SSE or death; †Patients who died without a prior SSE and ≥13 weeks after the last SSE assessment were censored at the last SSE assessment date. Patients alive at the survival cut-off date (15 February 2018) were censored at the last date known to be alive.
AAP, abiraterone acetate and prednisone/prednisolone; EBRT, external beam radiotherapy; ITT, intention-to-treat; SSE, symptomatic skeletal event.
Smith M *et al*. Presented at European Society for Medical Oncology; Munich, Germany; October 19–23, 2018.

Sobrevida Global (ITT)



OS	AAP + radium-223 N=401	AAP + placebo N=405
Deaths, n (%)	155 (39)	141 (35)
Median (95% CI), months	30.7 (25.8–NE)	33.3 (30.2–41.1)
HR (95% CI)	1.195 (0.950−1.505)	
P-value (2-sided)	0.1280	

Final OS analysis to be performed after 500 events

AAP, abiraterone acetate and prednisone/prednisolone; ITT, intention-to-treat; NE, not estimable; OS, overall survival.
Smith M *et al.* Presented at European Society for Medical Oncology; Munich, Germany; October 19–23, 2018.

Objetivos Secundários e Exploratórios

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	AAP + radium-223 N=401	AAP + placebo N=405	Hazard ratio (95% CI)
Secondary endpoints	**Median (95% CI), months**		
rPFS (central review)	11.2 (9.1–11.8)	12.4 (10.8–14.5)	1.152 (0.960–1.383)
Time to cytotoxic chemotherapy	29.5 (26.5–35.7)	28.5 (23.7–NE)	1.033 (0.816–1.308)
Time to opiate use for cancer pain	19.0 (14.4–23.2)	22.6 (18.0–25.7)	1.126 (0.921–1.378)
Exploratory endpoints			
Time to PSA progression	9.6 (8.2–10.8)	9.0 (7.9–10.1)	0.937 (0.792–1.108)
Time to deterioration in HRQoL*	9.5 (6.9–12.0)	10.5 (8.3–13.0)	1.079 (0.865–1.345)

*As reported in the safety population (AAP + radium-223 N=392, AAP + placebo N=394) during the treatment period using the National Comprehensive Cancer Network / Functional Assessment of Cancer Therapy prostate cancer index physical disease-related symptoms subscale.
AAP, abiraterone acetate and prednisone/prednisolone; HRQoL, health-related quality of life; NE, not estimable;
PSA, prostate-specific antigen; rPFS, radiological progression-free survival.

Eventos Adversos

TEAEs in ≥15% of patients in either group, n (%)	AAP + radium-223 N=392			AAP + placebo N=394		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Back pain	133 (34)	23 (6)	0	121 (31)*	16 (4)	0
Fatigue	89 (23)	4 (1)	0	79 (20)	6 (2)	0
Arthralgia	80 (20)	4 (1)	0	75 (19)	5 (1)	0
Fracture†	103 (26)	35 (9)	1 (0.3)	38 (10)*	12 (3)	0
Hypertension	59 (15)	43 (11)	0	78 (20)	51 (13)	1 (0.3)
ALT increased	69 (18)	29 (7)	5 (1)	59 (15)	28 (7)	0
Constipation	56 (14)	1 (0.3)	0	72 (18)	0	0
Diarrhoea	65 (17)	4 (1)	0	60 (15)	7 (2)	0
Nausea	66 (17)	1 (0.3)	0	59 (15)	1 (0.3)	0
AST increased	61 (16)	18 (5)	1 (0.3)	53 (14)	16 (4)	0
Peripheral oedema	51 (13)	2 (0.5)	0	61 (16)	0	0
Anaemia	57 (15)	24 (6)	0	46 (12)	11 (3)	0

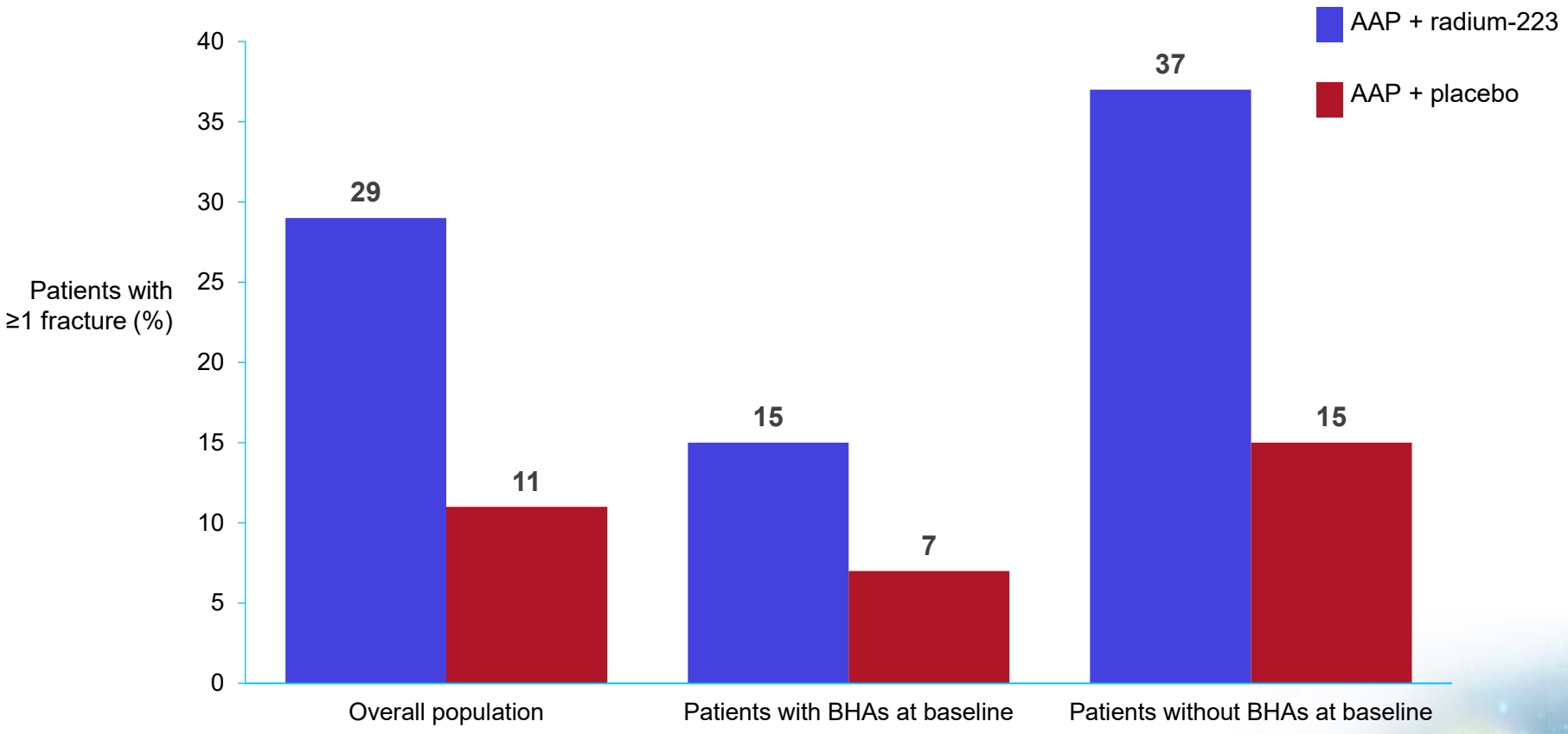
No grade 5 TEAEs reported in ≥10% of patients; *Grade of severity missing for one patient; †Compound term for events of femoral neck, femur, humerus, lumbar vertebral, osteoporotic, pathological, radius, rib, spinal compression, stress, thoracic vertebral, tooth, traumatic and ulna fracture.
AAP, abiraterone acetate and prednisone/prednisolone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Revisão independente dos eventos de fraturas*

	AAP + radium-223	AAP + placebo
Patients with ≥1 fracture, n	76	23
No bone metastasis at site of fracture, n	60	17
Type of fracture, n		
Pathological	19	6
Traumatic	27	13
Osteoporotic	37	4
Indeterminate	1	0

*Independent review of fractures was based on patients with fractures and available image scans: n=80 in AAP + radium-223 group, n=27 in AAP + placebo group.
AAP, abiraterone acetate and prednisone/prednisolone; BHA, bone health agent.

ERA 223 – Análise subgrupo de fraturas por uso prévio de inibidores de osteólise



AAP, abiraterone acetate and prednisone/prednisolone; BHA, bone health agent.

Risco de fratura aumentado em outros estudos clínicos em

Trial Active arm	Disease state	Fractures % (% using BHA)	
		Experimental	Placebo
SPARTAN[1] Apalutamide	nmCRPC	11.7 (10.2)	6.5 (9.7)
PROSPER[2] Enzalutamide	nmCRPC	9.8 (nr)	4.9 (nr)
PREVAIL[2] Enzalutamide	mCRPC	8.8 (nr)	3.0 (nr)
AFFIRM[2] Enzalutamide	mCRPC	4.0 (nr)	0.8 (nr)
COU-301[3] Abiraterone	mCRPC	5.9 (nr)	2.3 (nr)
COU-302[3] Abiraterone	mCRPC	No data	

- Treatment arms have higher fracture rates than placebo arms
- nmCRPC has higher fracture rates than mCRPC, possibly due to longer duration of follow-up
- Little information on use of BHA in these trials
- Fracture data from COU-302 might be informative with respect to understanding ERA 223

nr, not reported.

1. Smith MR *et al. N Engl J Med* 2018;378:1408–1418. 2. Xtandi (enzalutamide) [prescribing information]. Astellas Pharma US, Inc., Northbrook, IL. July 2018.
3. Zytiga (abiraterone acetate) [prescribing information]. Janssen Biotech, Inc., Horsham, PA. February 2018.

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Por que os resultados do ERA-223 são tão diferentes do ALSYMPCA?

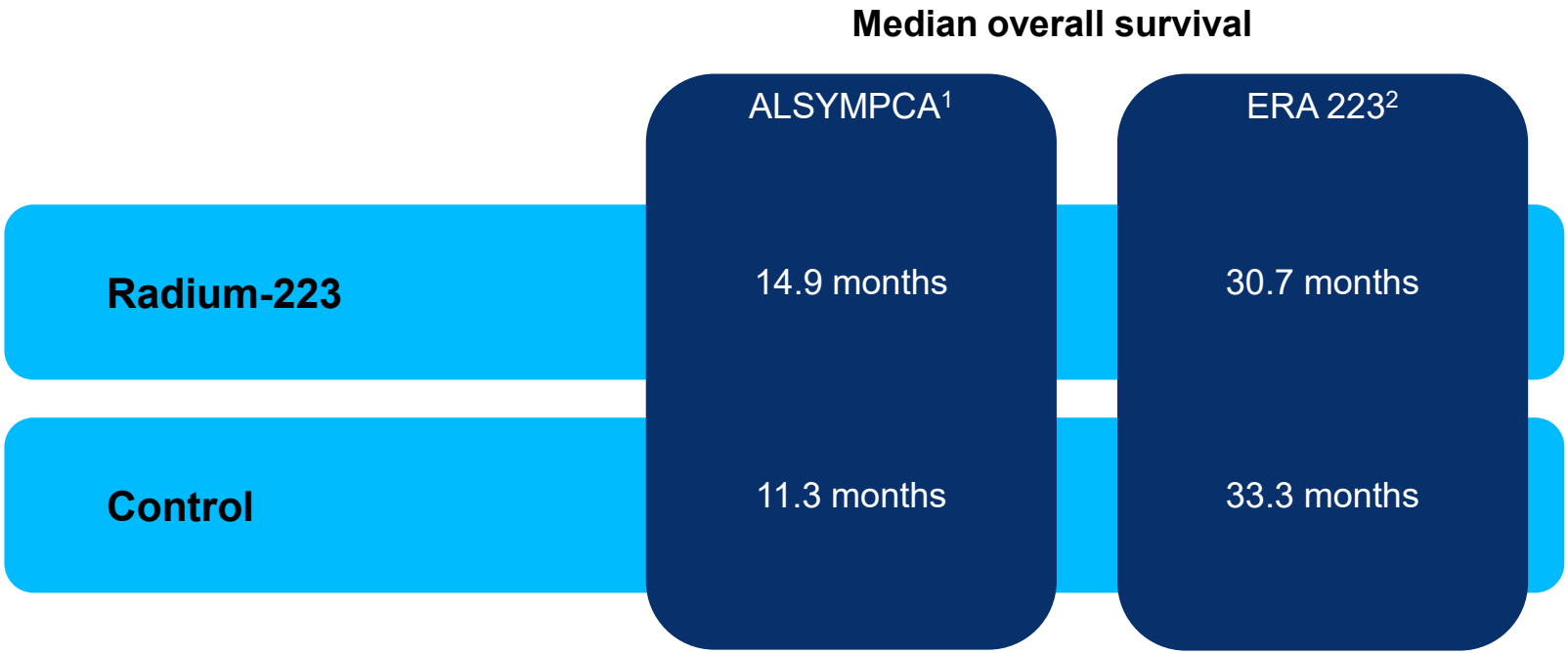
Características basais diferentes

	ALSYMPCA[1]	ERA 223[2]
Prior docetaxel	57%	0%
Asymptomatic	2%	52%
Concomitant steroid use	<50%	100%
LDH, PSA, and ALP levels	Higher	Lower

ALP, alkaline phosphatase; BPI-SF, brief pain inventory-short form; LDH, lactate dehydrogenase; PSA, prostate-specific antigen.

1. Parker C *et al. Eur Urol.* 2016;70:875–883. 2. Smith M *et al.* Presented at European Society for Medical Oncology; Munich, Germany; October 19–23, 2018.

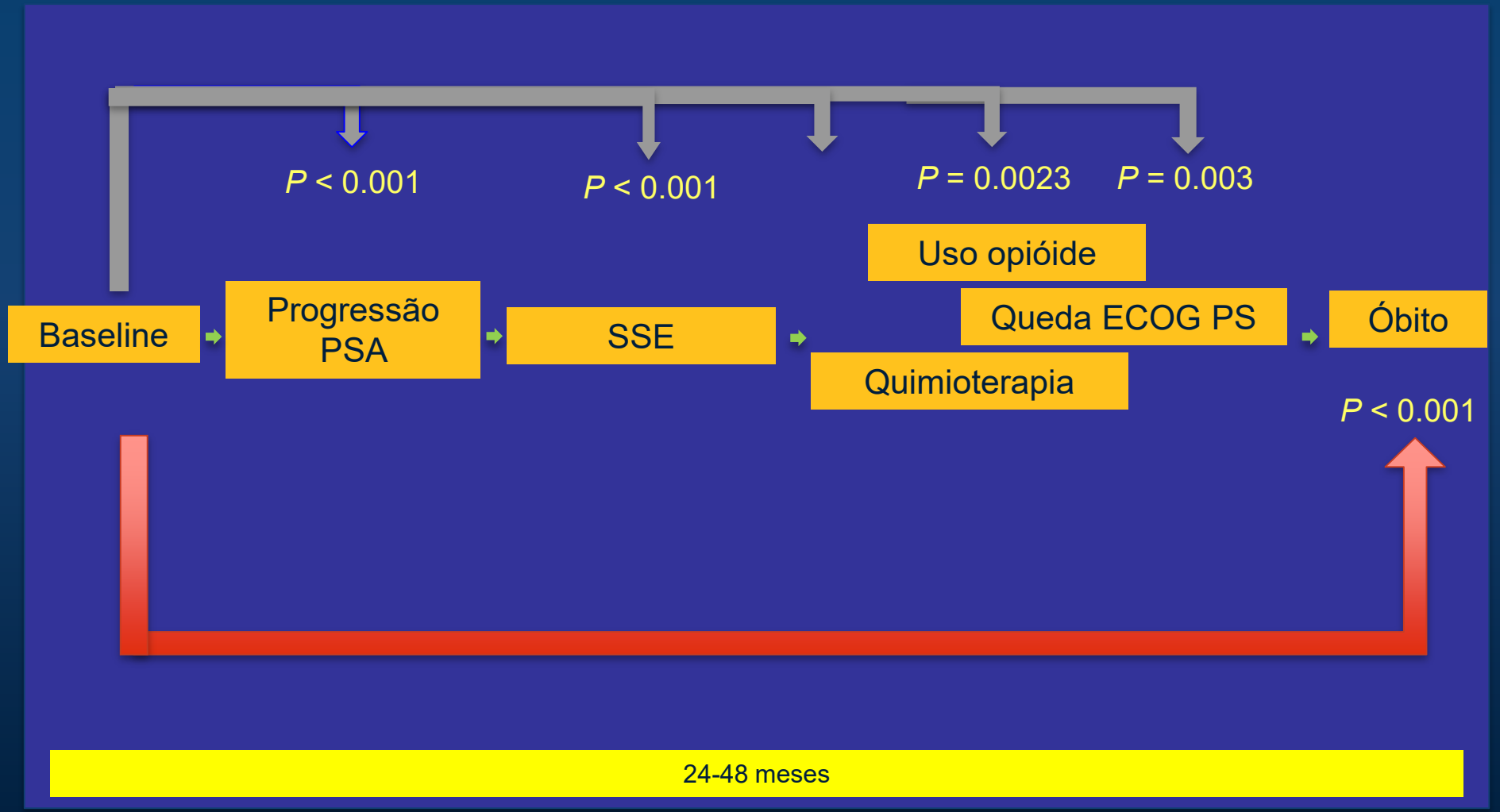
Sobrevida Global diferente



- ALSYMPCA patients are treated at a later stage in the course of mCRPC
  - Disease characteristics
  - Prior therapies
  - Median OS
- Median OS differences significant between arms of ALSYMPCA but not ERA-223

1. Parker C *et al. N Engl J Med.*. 2013;369:213–223. 2. Smith M *et al.* Presented at European Society for Medical Oncology; Munich, Germany; October 19–23, 2018.

Benefício em múltiplos objetivos



CONCLUSÕES – Rádio 223

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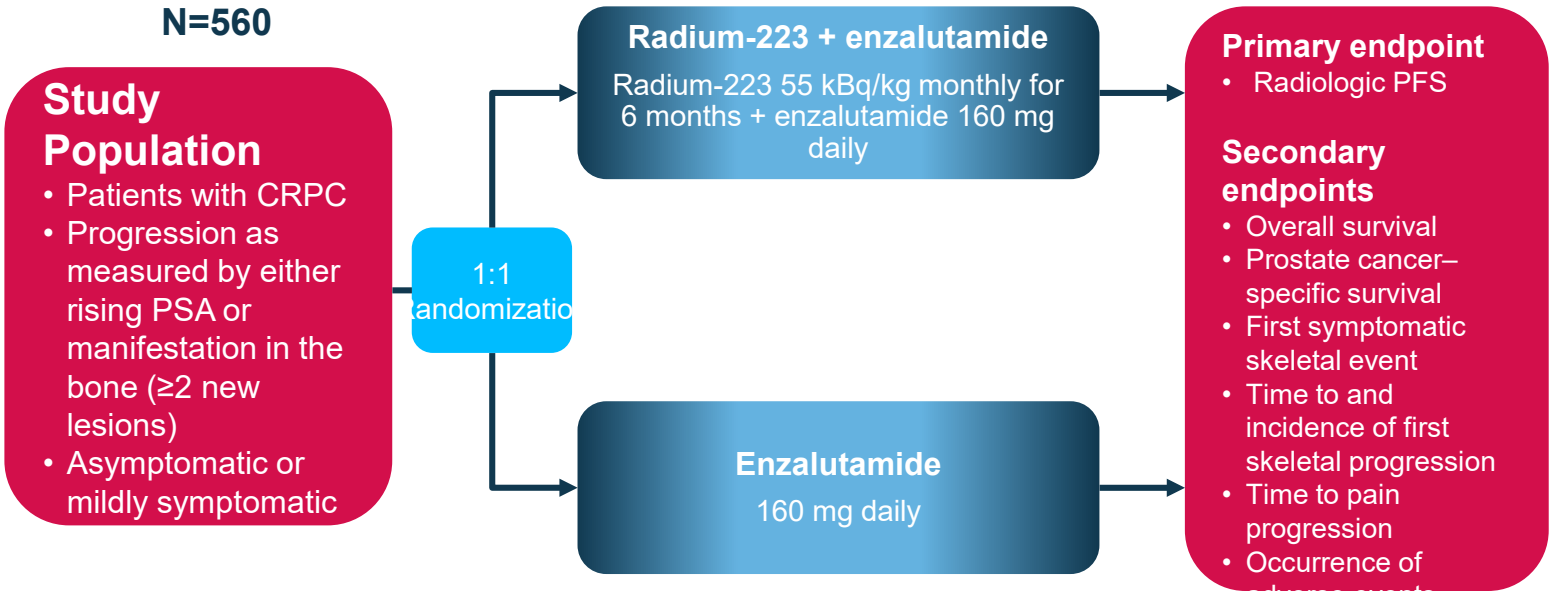
- Aumento de SG (HR 0,70), e em todos os objetivos secundários
- Perfil de toxicidade favorável
- Prolonga o tempo para o primeiro SSE (HR 0,66)
- Inibidores de osteólise são essenciais para prevenção de SSE e redução de osteoporose
- Uso concomitante com Abiraterona é contra-indicado
- Estudo PEACE-III avaliando concomitancia com Enzalutamida está em andamento.

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



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.