ASCO 2012 Genitourinary Cancers Symposium

The ROYAL MARSDEN NHS Foundation Trust

Overall Survival Benefit and Safety Profile of Radium-223 Chloride (Alpharadin), A First-in-Class Alpha-Pharmaceutical: Results from a Phase III Randomized Trial (ALSYMPCA) in Patients With Castration-Resistant Prostate Cancer (CRPC) With Bone Metastases

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Disclosures

- C. Parker has served in a consultant or advisory role for Algeta ASA (uncompensated) and Bayer
- D. Heinrich, S. Nilsson, N.D. James, and O. Sartor have served in consultant or advisory roles for Algeta ASA
- C.G. O'Bryan-Tear is employed by and has an ownership interest in Algeta ASA
- J. Garcia-Vargas is an employee of Bayer HealthCare Pharmaceuticals
- J.M. O'Sullivan, S. Fosså, A. Chodacki, T. Demkow, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, A. Solberg, I. Syndikus, and A. Cross have nothing to disclose

Acknowledgments

All patients who participated in the study, and their caregivers

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Massimo Aglietta
Dino Amadori
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Javier Arbizu
Amit Bahl
Vladimir Balaz
Pilar Bello
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Paul Verhagen
Nicholas Vogelzang
Wolfgang von Pokrzywnitzki
Steffen Alexander Wedel
Anders Widmark
Pawel Jan Wiechno
Sibylle Böhmer
Henry Woo
Tsz Kok Yau
Kwok Keung Yuen
Roman Zachoval
Romuald Zdrojowy

ALSYMPCA was sponsored by Algeta ASA and Bayer Healthcare Pharmaceuticals.

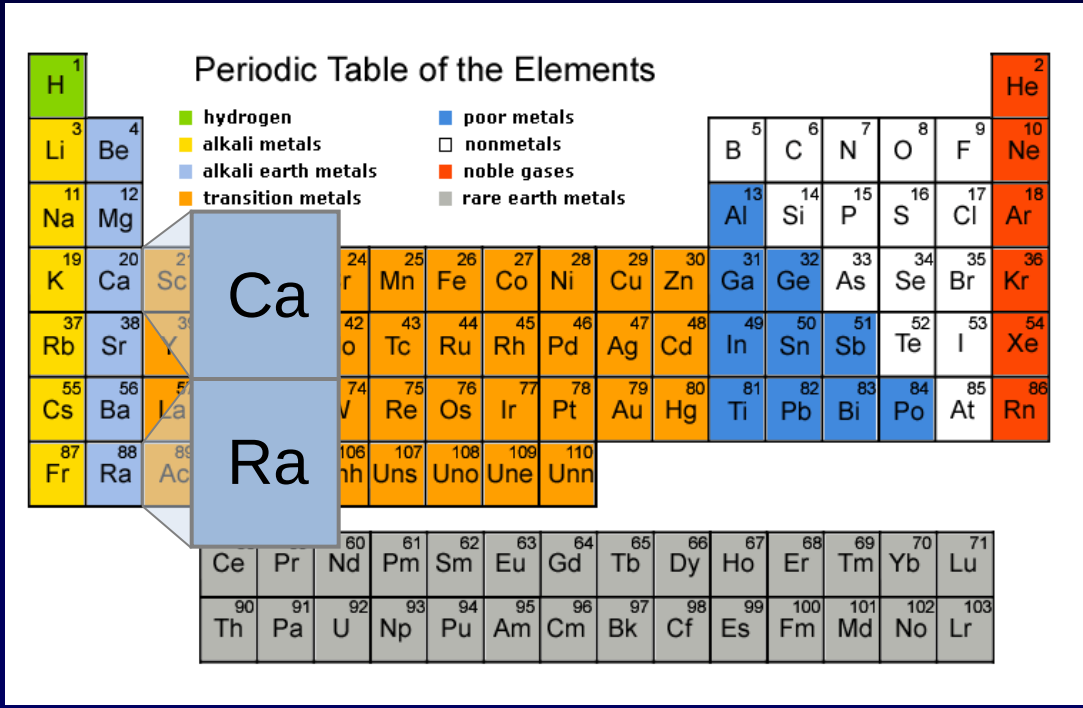
Background and Rationale

- **> 90% of patients with metastatic CRPC have radiologic evidence of bone metastases[1]**
- **Skeletal-related events (SREs) include spinal cord compression, pathological fracture, and need for surgery or EBRT[2]**
- **Bone metastases are a major cause of death, disability, decreased quality of life, and increased treatment cost[3]**
- **Current bone-targeted therapies have not been shown to improve survival**

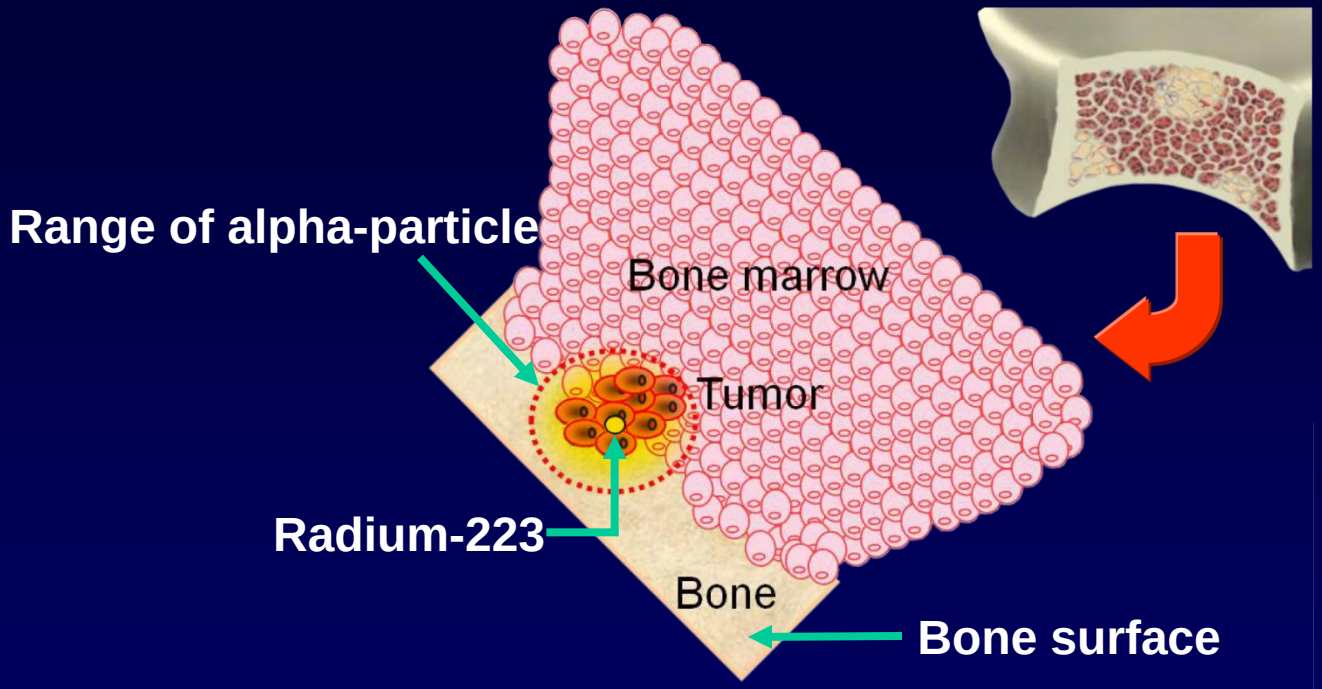
1. Tannock et al. *N Engl J Med.* 2004;351:1502-1512.
2. Lipton. *Semin Oncol.* 2010;37:S15-S29.
3. Lange and Vasella. *Cancer Metastasis Rev.* 1999;17:331-336.

Radium-223 Targets Bone Metastases

- Radium-223 acts as a calcium mimic
- Naturally targets new bone growth in and around bone metastases
- Radium-223 is excreted by the small intestine



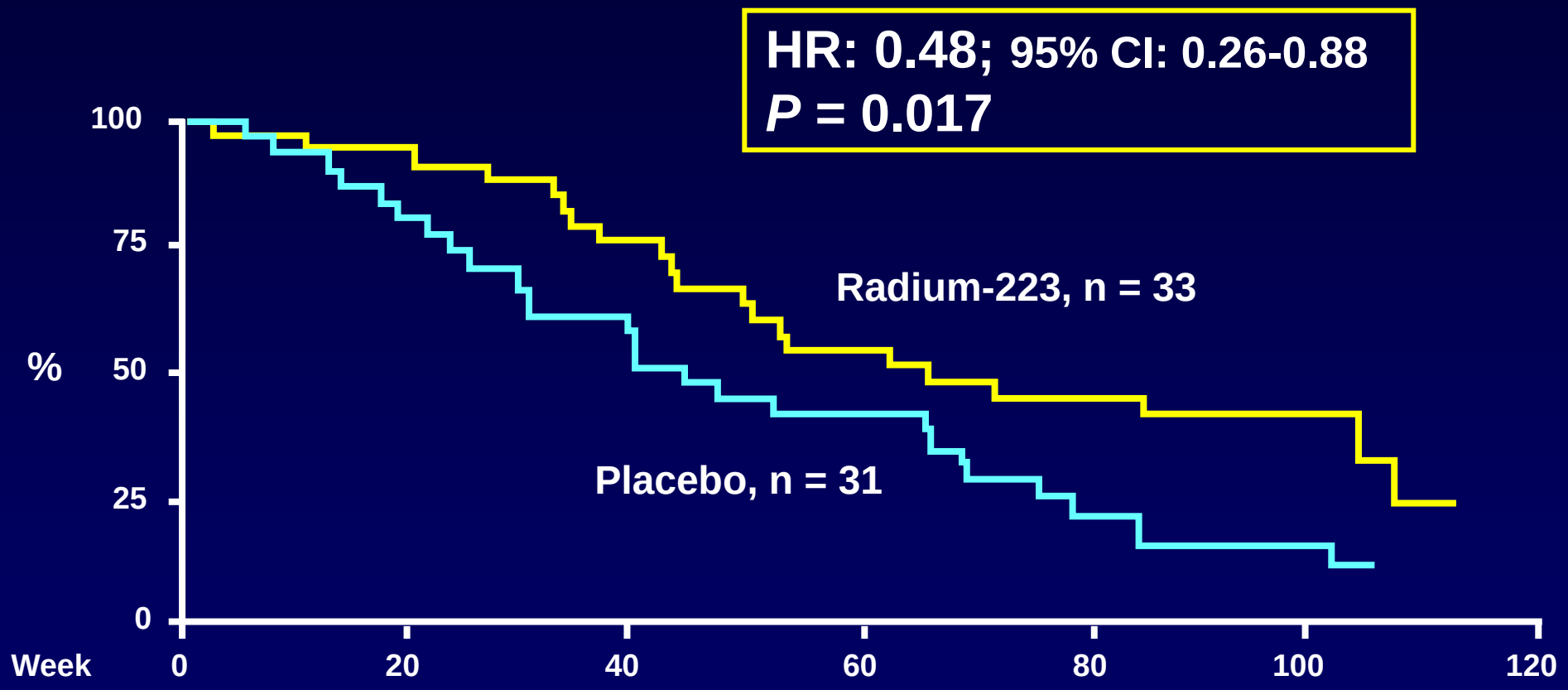
Radium-223 Targets Bone Metastases



- **Alpha-particles induce double-strand DNA breaks in adjacent tumour cells[1]**
  - **Short penetration of alpha emitters (2-10 cell diameters) = highly localised tumour cell killing and minimal damage to surrounding normal tissue**

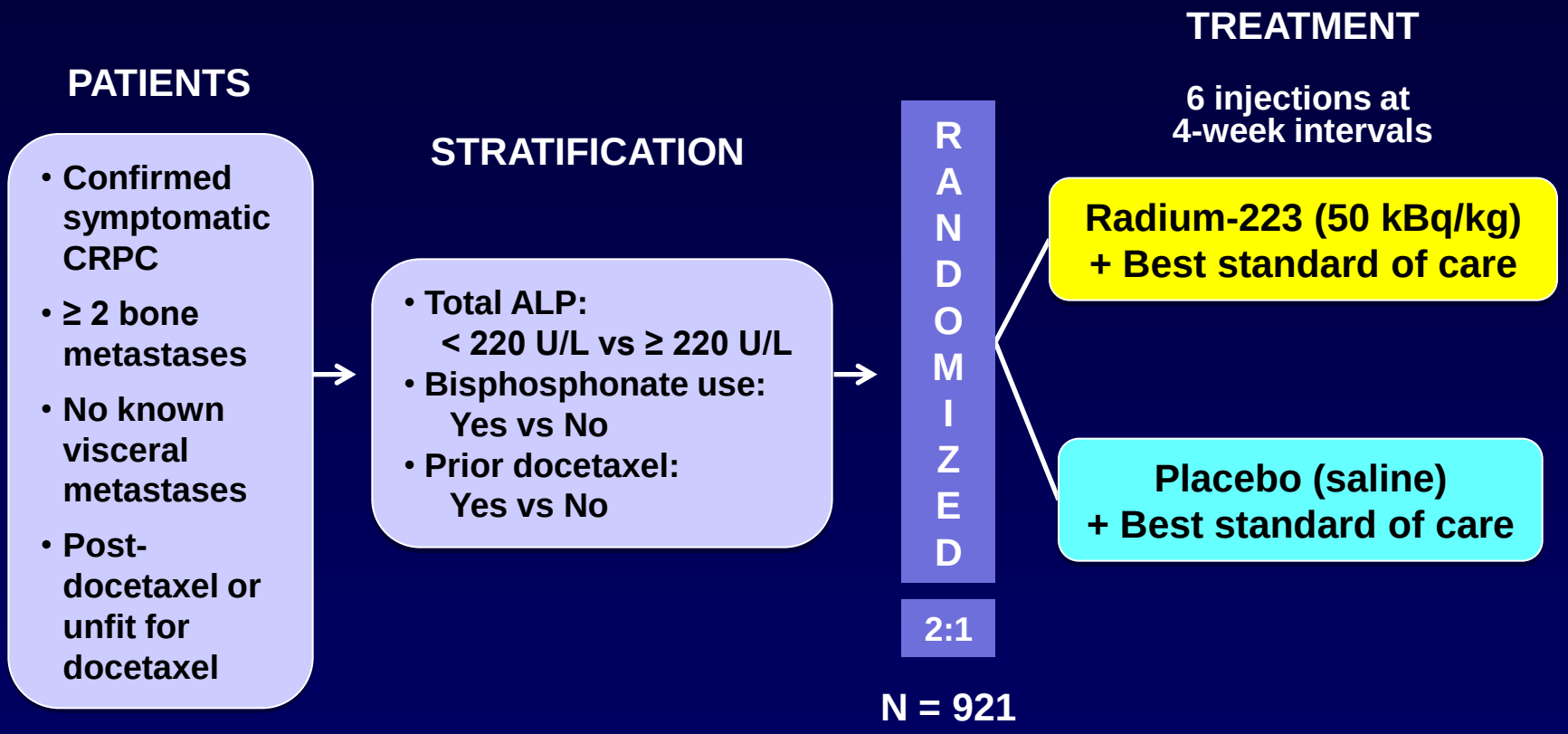
1. Perez et al. *Principles and Practice of Radiation Oncology.* 5th ed. Lippincott Williams & Wilkins; 2007:103.

Radium-223 Improved Overall Survival in the Placebo-Controlled Phase II Study in CRPC



Nilsson. *Lancet Oncol*. 2007;8:587-594.

ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design



Planned follow-up is 3 years

Clinicaltrials.gov identifier: NCT00699751.

ALSYMPCA Study Endpoints

- Primary Endpoint
  - Overall survival

- Main Secondary Endpoints
  - Time to first SRE
  - Time to total ALP progression
  - Total ALP response
  - Total ALP normalization
  - Time to PSA progression
  - Safety
  - Quality of life

ALSYMPCA Statistical Design

- **Statistical assumption**
  - **90% power**
  - **HR = 0.76**
  - **0.05 two-sided alpha**

	Planned Interim Analysis	Final Analysis
Events	320	640
Alpha	0.00306	0.05

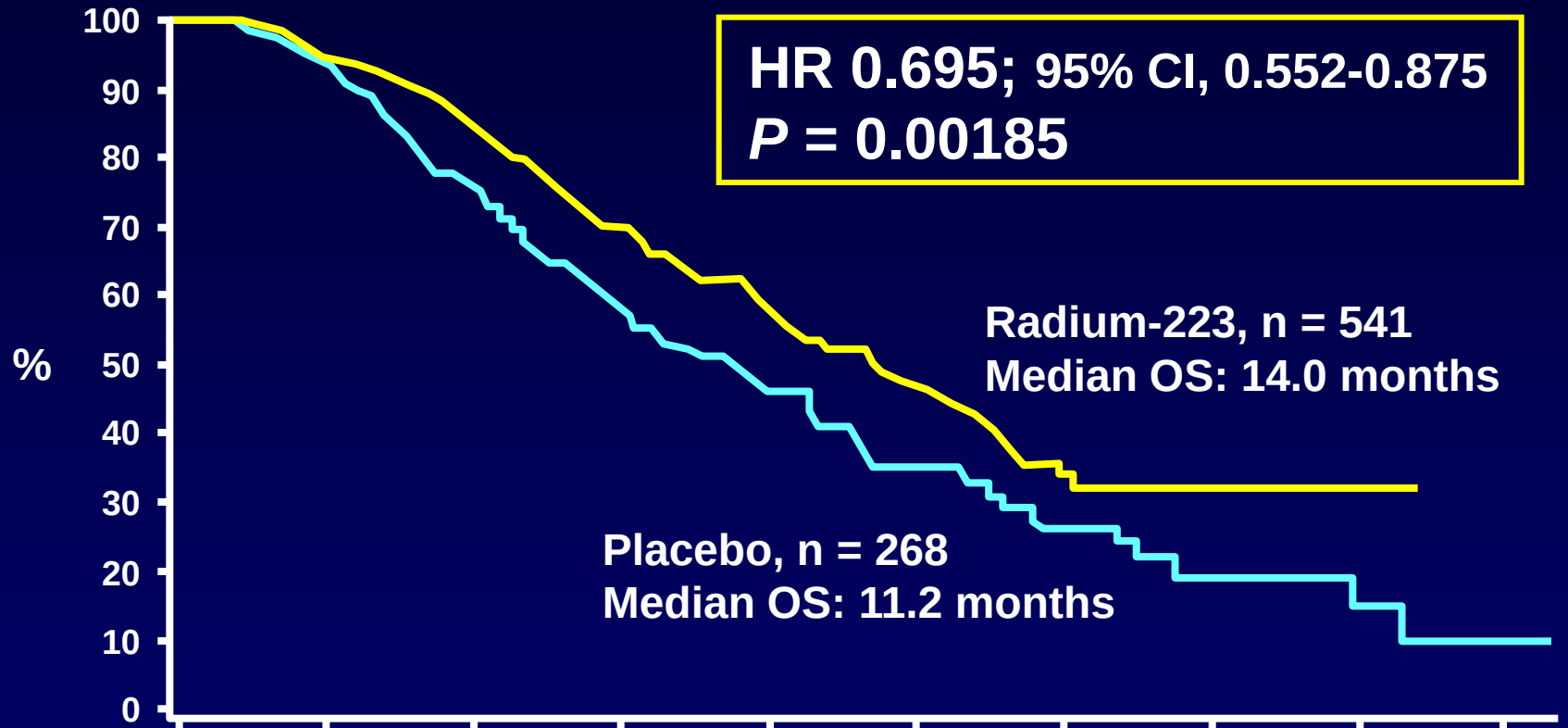
ALSYMPCA Patient Demographics and Baseline Characteristics (ITT; N = 809)

Parameter	Radium-223 (n = 541)	Placebo (n = 268)
Age, y		
Mean	70.2	70.7
Race, n (%)		
Caucasian	507 (94)	252 (94)
Baseline ECOG score, n (%)		
≤ 1	467 (86)	229 (85)
2	71 (13)	37 (14)
Extent of disease, n (%)		
< 6 metastases	88 (16)	33 (12)
6-20 metastases	235 (44)	129 (48)
> 20 metastases/superscan	217 (40)	106 (40)
WHO ladder, cancer pain index ≥ 2, n (%)	294 (54)	142 (53)

ALSYMPCA Patient Baseline Characteristics, cont (ITT; N = 809)

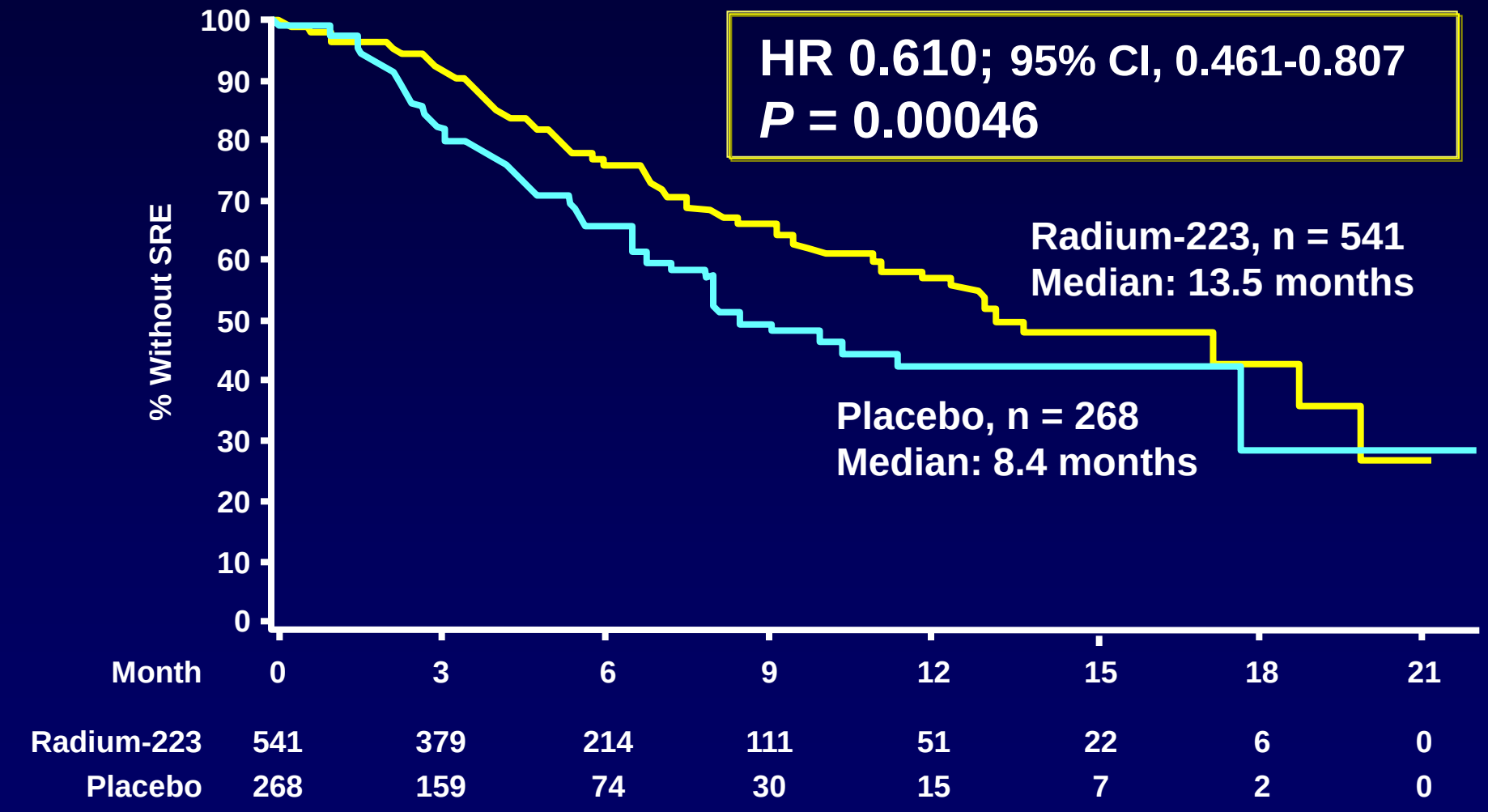
Parameter Median (min, max)	Radium-223 (n = 541)	Placebo (n = 268)
Hemoglobin, g/dL	12.2 (8.5-15.7)	12.1 (8.4-16.4)
Albumin, g/L	40 (24-53)	40 (23-50)
Total ALP, µg/L	213 (32-4661)	224 (29-3225)
LDH, U/L	317 (76-2171)	328 (132-3856)
PSA, µg/L	159 (3.78-6026)	195 (1.5-14500)

ALSYMPCA Overall Survival



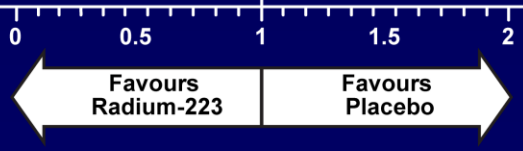
Month	0	3	6	9	12	15	18	21	24	27
Radium- 223	541	450	330	213	120	72	30	15	3	0
Placebo	268	218	147	89	49	28	15	7	3	0

ALSYMPCA Time to First Skeletal-Related Event



Time to First Skeletal-Related Event by ALSYMPCA Stratification Factors

Variable	Subgroup	N	HR	95% CI
All Patients		809	0.610	0.461–0.807
Total ALP	< 220 U/L	452	0.513	0.358–0.735
	≥ 220 U/L	357	0.828	0.534–1.284
Current Use of Bisphosphonates	Yes	331	0.464	0.288–0.748
	No	478	0.715	0.507–1.009
Prior Use of Docetaxel	Yes	470	0.561	0.400–0.788
	No	339	0.730	0.450–1.186



ALSYMPCA Time to First SRE Component

	No. (%) of Patients		Time to First Event (Radium-223 vs Placebo)	
SRE Component	Radium-223 (n = 541)	Placebo (n = 268)	*P* value*	HR (95%CI)
External Beam Radiotherapy	122 (23)	72 (27)	0.0038	0.65 (0.48-0.87)
Spinal Cord Compression	17 (3)	16 (6)	0.016	0.44 (0.22-0.88)
Pathologic Bone Fracture	20 (4)	18 (7)	0.013	0.45 (0.24-0.86)
Surgical Intervention	9 (2)	5 (2)	0.69	0.80 (0.27-2.4)

*Not adjusted for multiplicity

Sartor. ASCO GU 2012 Poster Presentation. Abstract 9.

ALSYMPCA Secondary Endpoints: ALP and PSA

	Hazard ratio 95% CI	P-value
Time to Total ALP progression	0.163 (0.121 – 0.221)	< 0.00001
Time to PSA progression	0.671 (0.546 – 0.826)	0.00015

	Radium-223 n (%)	Placebo n (%)	P-value
Total ALP response (30% reduction)	165 (43)	4 (3)	< 0.001
Total ALP normalization*	83 (33)	1 (1)	< 0.001

*In patients who had elevated total ALP at baseline.

ALSYMPCA Summary of Patients With Adverse Events: Safety Population* (N = 762)

Patients With Adverse Events (AEs), n (%)	Radium-223 (n = 509)	Placebo (n = 253)
All grade AEs	450 (88)	237 (94)
Grade 3 or 4 AEs	257 (51)	150 (59)
Serious AEs (SAEs)	220 (43)	139 (55)
Discontinuation due to AEs	68 (13)	51 (20)

*Patients who received at least 1 injection.

ALSYMPCA Adverse Events of Interest

Patients With AEs, n (%)	All Grades		Grades 3 or 4	
	Radium-223 (n = 509)	Placebo (n = 253)	Radium-223 (n = 509)	Placebo (n = 253)
Hematologic				
Anemia	136 (27)	69 (27)	54 (11)	29 (12)
Neutropenia	20 (4)	2 (1)	9 (2)	2 (1)
Thrombocytopenia	42 (8)	14 (6)	22 (4)	4 (2)
Non-Hematologic				
Bone pain	217 (43)	147 (58)	89 (18)	59 (23)
Diarrhea	112 (22)	34 (13)	6 (1)	3 (1)
Nausea	174 (34)	80 (32)	8 (2)	4 (2)
Vomiting	88 (17)	32 (13)	10 (2)	6 (2)
Constipation	89 (18)	46 (18)	6 (1)	2 (1)

Conclusions

In CRPC patients with bone metastases:

- **Radium-223 significantly prolonged OS**
  - ***P* value = 0.00185; HR = 0.695; 95% CI, 0.552-0.875**
- **Radium-223 significantly prolonged time to first SRE**
  - ***P* value = 0.00046; HR = 0.610; 95% CI, 0.461-0.807**
- **Radium-223 significantly prolonged time to the SRE components external beam radiotherapy, spinal cord compression, and pathologic bone fracture**
- **Radium-223 was very well tolerated**

Radium-223, a novel alpha-pharmaceutical, may provide a new standard of care for the treatment of CRPC patients with bone metastases