# Radioisoopes in the Treatment of Advanced Prostate Cancer

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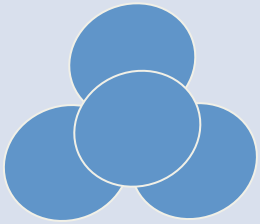
# Characteristics of Radioisotopes

| | Alpha Particles[1] | Beta Particles[2] |
|---|---|---|
| **Size** |  |  |
| **Definition** | Consists of helium nuclei<br>High LET<br>Do not penetrate a sheet of paper | Consists of electrons<br>Relatively low LET<br>May be halted by an aluminum plate |
| **DNA hits to kill cells** | 1-10 | 100-1000 |
| **Type of DNA Damage** | Double-strand breaks (Lethal, more difficult to repair)[3] | Single-strand breaks (More repairable) [3] |

LET = linear energy transfer

Sponsored by:

1. Henriksen G, et al. *J Nucl Med*. 2003;44(2):252-259; 2. Bruland OS, et al. *Clin Cancer Res.* 2006;12(20):6250s-6257s

# FDA-Approved Bone-Targeting Radionuclides for the Treatment of Bone Metastases

| FDA Approval | Bone Agent | Indication |
|---|---|---|
| March 1997 | Samarium-153-lexidronam | Relief of bone pain in patients with painful skeletal metastases |
| June 1993 | Strontium-89 | Relief of pain in patients with confirmed osteoblastic metastatic bone lesions |

Sartor. *Urology*. 2004;63:940; Porter. *Int J Radiation Oncology Biol Phys*. 1993;25:805; Quadramet [package insert]. Princeton, NJ: EUSA Pharma, Inc.; 2008; Metastron [package insert]. Arlington Heights, IL: Medi-Physics, Inc.; 1998; U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed September 15, 2010; U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed September 15, 2010.

# Bone-Targeting Radionuclides for Patients With Prostate Cancer Bone Metastases

| Trial | Bone Agent | No. of Pts | Results |
|---|---|---|---|
| Sartor, 2004 phase III | Samarium-153-lexidronam | 101 | <u>Improvement over placebo</u>:<br>VAS: 2-4 wks (*P*≤0.05)<br>PDS: 1-4 wks (*P*≤0.05)<br>Analgesic use: 3-4 wks (*P*<0.0284) |
| | Placebo | 51 | |
| Porter, 1993 phase III | Strontium-89 + EBR | 126 | <u>Strontium-89 vs placebo:</u><br>New painful sites: 0.587 vs 1.213 (*P*<0.002)<br>Analgesic free at 3 mos: 17.1% vs 2.4% (*P*<0.05)<br>Time to further RT: 35.3 vs 20.3 wks (*P*=0.006) |
| | Placebo + EBR | | |
| Nilsson, 2007 phase II | Radium-223 + EBR | 33 | <u>Radium-223 vs placebo</u>:<br>Change in bone ALP: -65.6% vs 9.3% *P*<0.0001<br>Median time to PSA progression: 26 vs 8 wks (*P*=0.048)<br>Median OS: 65.3 vs 46.4 weeks (*P*=0.066) |
| | Placebo + EBR | 31 | |

ALP=alkaline phosphatase; PDS=pain descriptor scale (nonlinear); RT=radiotherapy; VAS=100-mm pain intensity visual analog scale (linear).

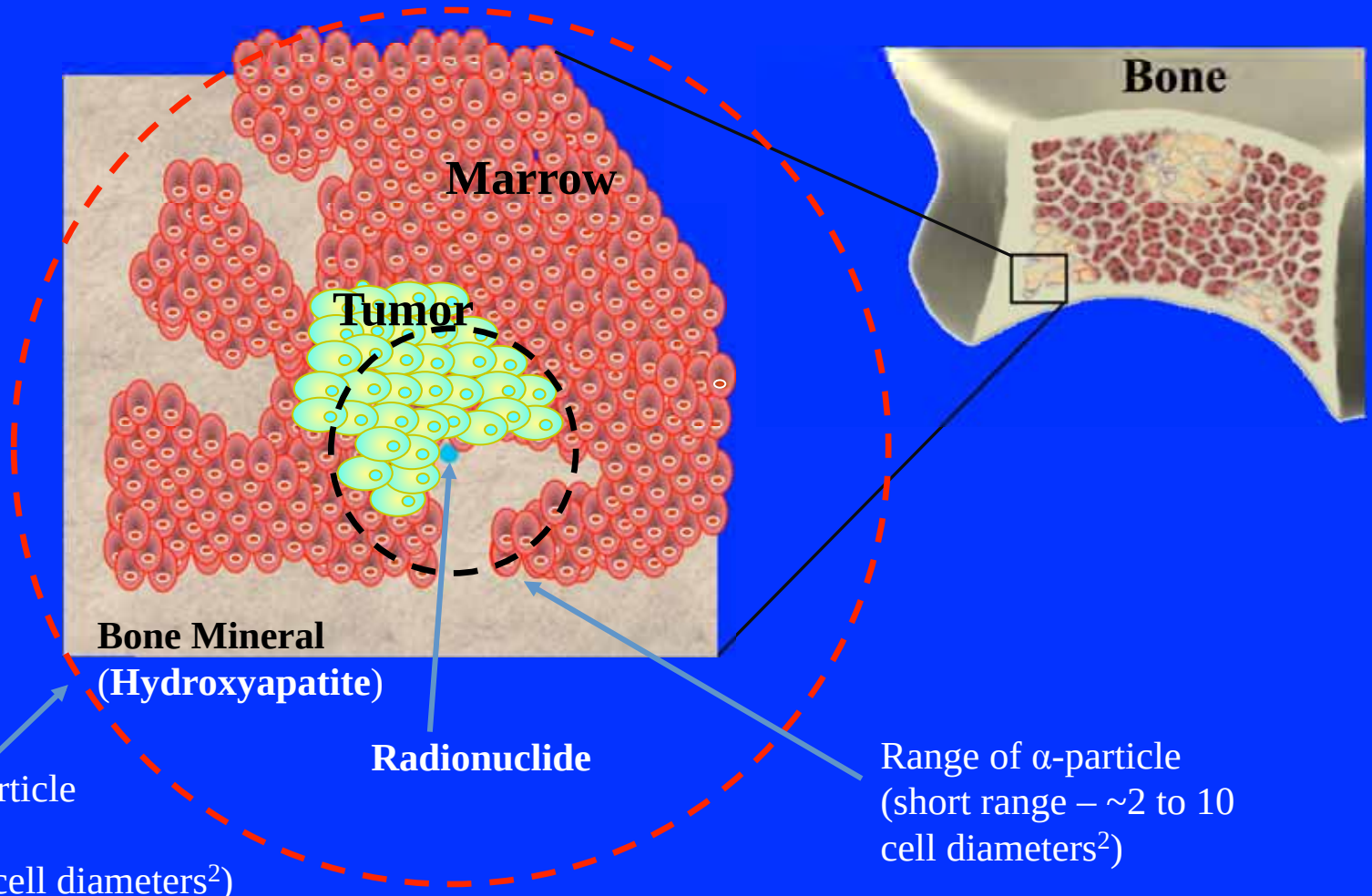
Sartor. *Urology*. 2004;63:940; Nilsson. *Lancet Oncol*. 2007;8:587; Porter. *Int J Radiation Oncology Biol Phys*. 1993;25:805.

# Mechanisms of Bone Targeting

- **Strontium-89: A calcium homologue, tracks deposition of calcium**
- **Samarium-153 EDTMP: Samarium does not track to bone, but when chelated with EDTMP the phosphonic acid groups target to areas of newly deposited bone**
- **Phosphorus-32: Tracks inorganic phosphorus in the body**

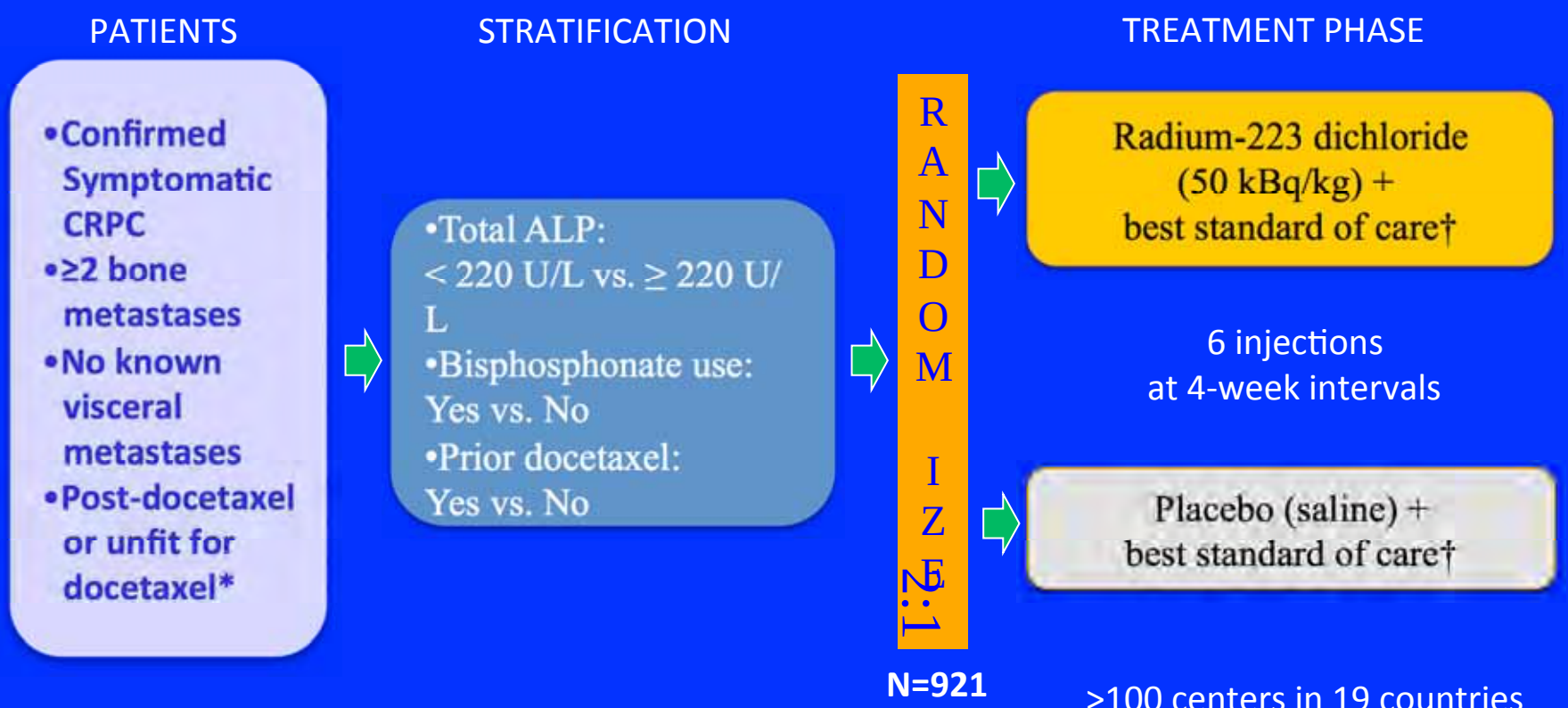
# Range of an α-emitting Radiopharmaceutical Compared to a β-emitter

Short range of α-particles could reduce bone marrow exposure[1]




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

# ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design[1]




*Unfit for docetaxel includes patients who were ineligible for docetaxel, refused docetaxel, or lived where docetaxel was unavailable

†Best standard of care defined as a routine standard of care at each center, eg. local external beam radiotherapy, corticosteroids, anti-androgens, estrogens (e.g., stilbestrol), estramustine, or ketaconazole

**Reference: 1.** Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

# ALSYMPCA Endpoints

| **Primary endpoint** |
| --- |
| • **Overall survival** |
| **Secondary endpoints** |
| • Time to occurrence of first SRE<br>• Time to total ALP progression<br>• Total ALP response<br>• Total ALP normalization<br>• Time to PSA progression<br>• Safety<br>• Quality of life |

**Reference:** Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

# ALSYMPCA
## *Major Inclusion/Exclusion Criteria*

**Inclusion criteria**

- Symptomatic CRPC with ≥2 bone metastases
  - Confirmed by bone scintigraphy
  - No known visceral metastases
- Regular analgesic medication use for cancer-related bone pain or treatment with EBRT for bone pain within previous 12 weeks
- Life expectancy of ≥6 months

**Exclusion criteria**

- Eligible for first course of docetaxel (i.e., fit, willing, and where docetaxel is available)
- Treatment with cytotoxic chemotherapy within previous 4 weeks or planned during the treatment period
- Failure to recover from AEs due to cytotoxic chemotherapy
- Prior use of systemic radiopharmaceuticals for bone metastases

**Reference:** Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

EBRT, external beam radiation therapy.

# ALSYMPCA : Patient Demographics and Baseline Characteristics

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

ITT group (n = 921)

WHO pain relief ladder:
1 – Non-opioid analgesic ± adjuvant
2 – Opioid for mild to moderate pain ± non-opioid analgesic ± adjuvant
3 – Opioid for moderate to severe pain ± non-opioid analgesic ± adjuvant
Patients may have also received external-beam radiation therapy for pain

**Reference:** Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

# ALSYMPCA: Patient Baseline Characteristics

| Parameter<br>Median (min, max) | Radium-223 dichloride (n = 614) | Placebo (n = 307) |
|---|---|---|
| Hemoglobin, g/dL | 12.2 (8.5-15.7) | 12.1 (8.5-16.4) |
| Albumin, g/L | 40 (24-53) | 40 (23-50) |
| Total ALP, µg/L | 211 (32-6431) | 223 (29-4805) |
| LDH, U/L | 315 (76-2171) | 336 (132-3856) |
| PSA, µg/L | 146 (3.8-6026) | 173 (1.5-14500) |
| Current bisphosphonates<br>Yes, n (%) | <br>250 (40.7) | <br>124 (40.4) |
| Prior docetaxel<br>No, n(%)<br>Yes, n (%) | <br>262 (42.7)<br>352 (57.3) | <br>133 (43.3)<br>174 (56.7) |

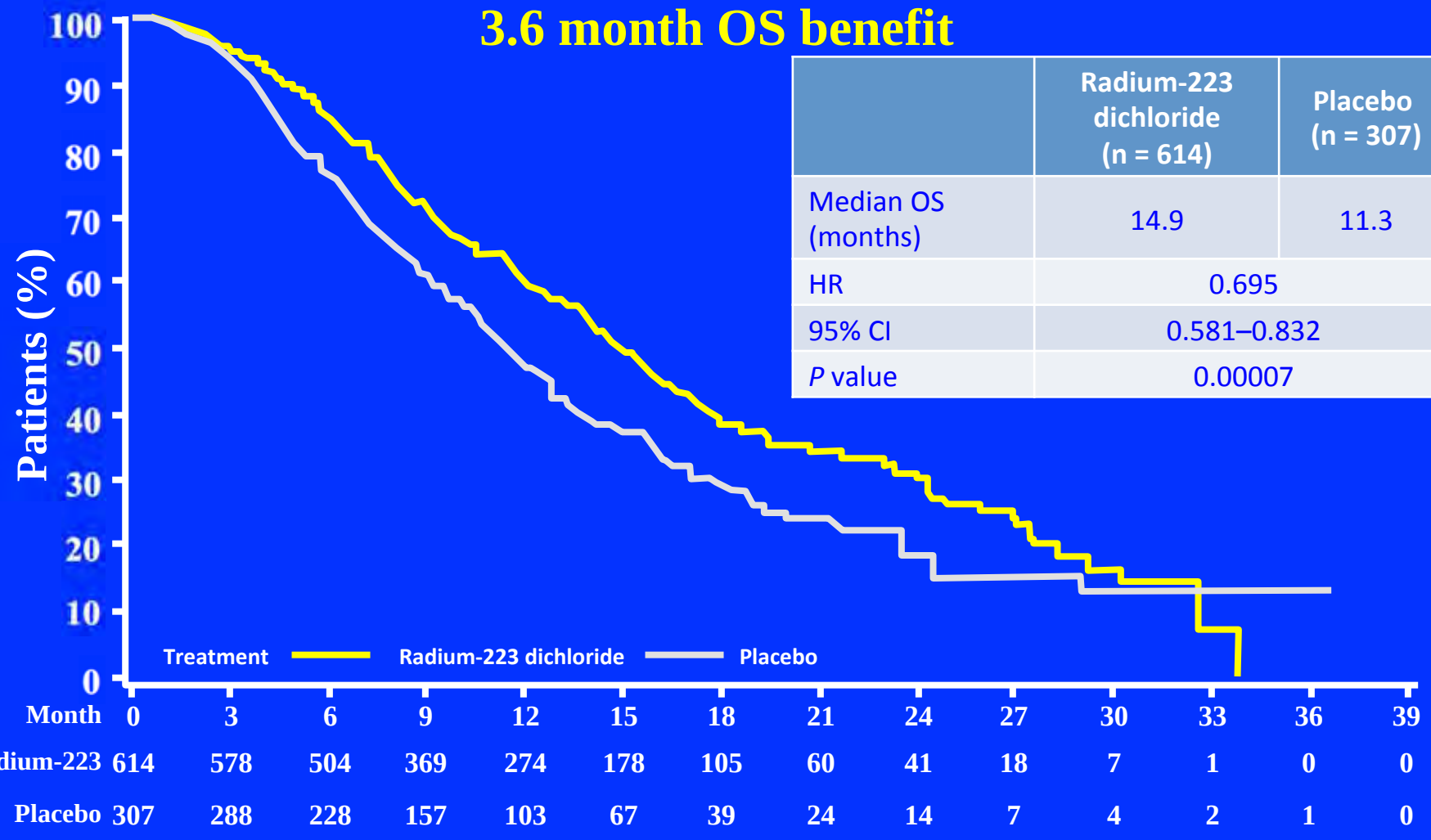
ITT group (n = 921)

**Reference:** Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

# ALSYMPCA Updated Analysis: Overall Survival

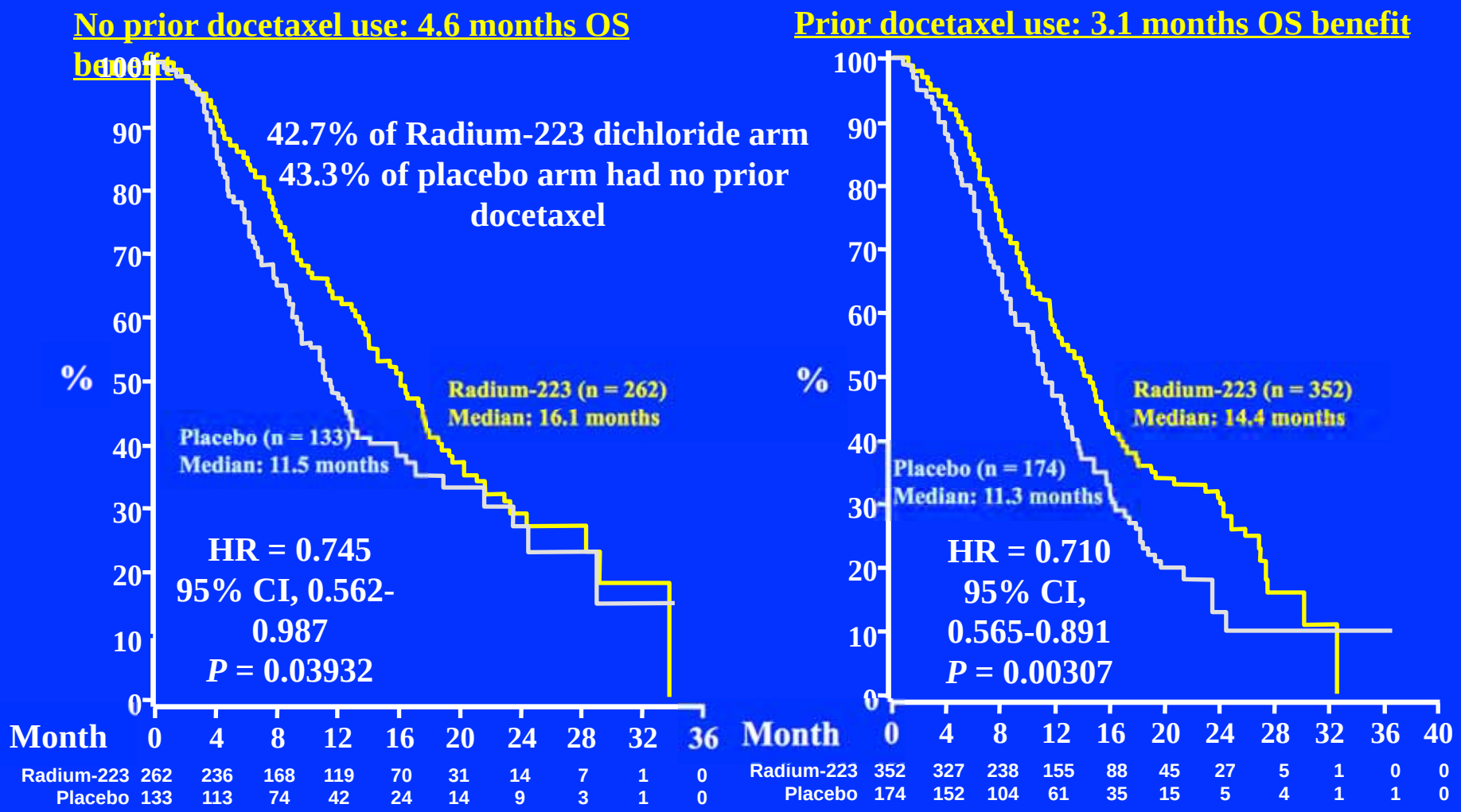
**3.6 month OS benefit**

| | Radium-223 dichloride (n = 614) | Placebo (n = 307) |
|---|---|---|
| Median OS (months) | 14.9 | 11.3 |
| HR | 0.695 | |
| 95% CI | 0.581–0.832 | |
| *P* value | 0.00007 | |



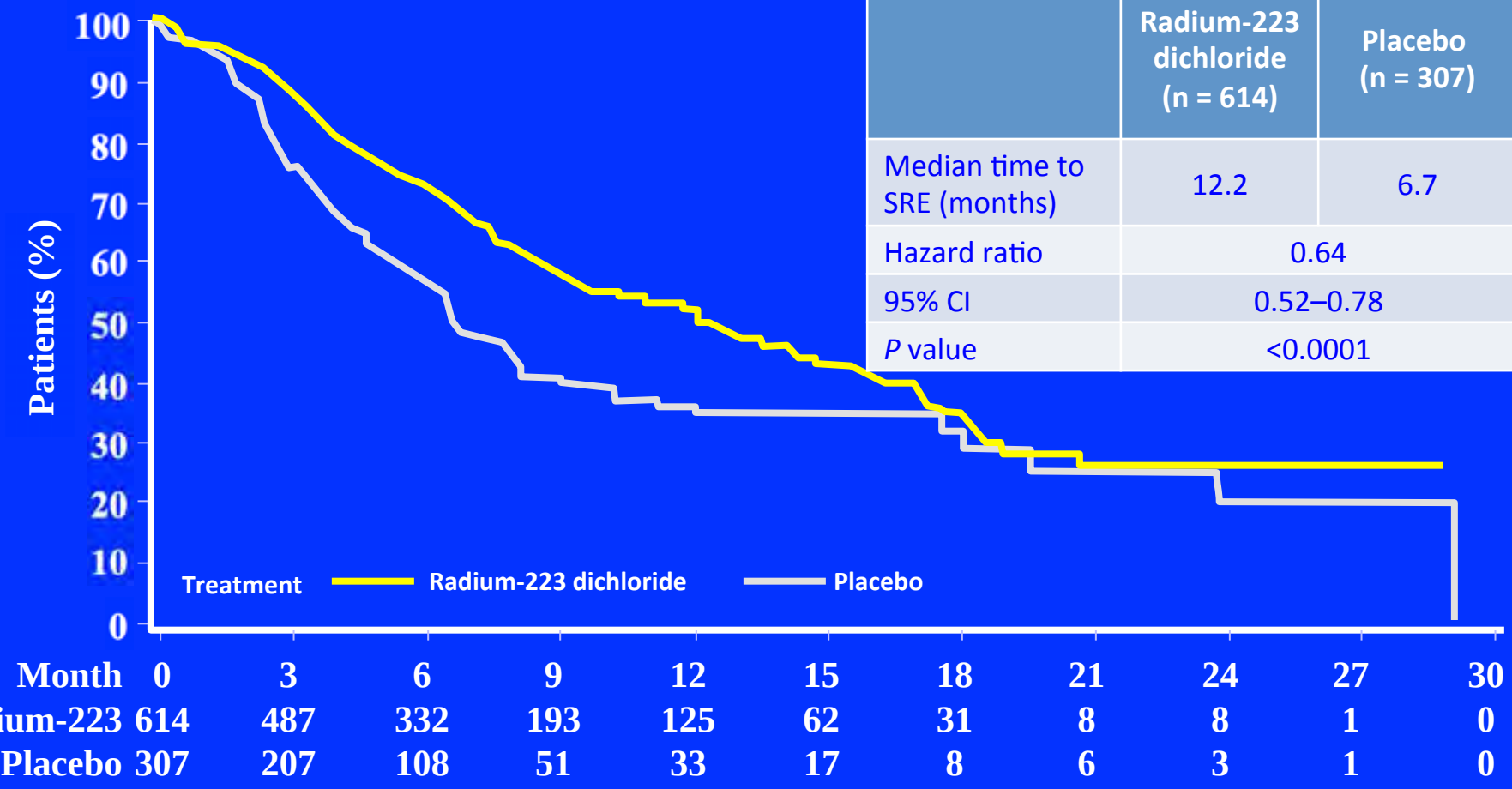

**Reference:** Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

# ALSYMPCA : Overall Survival Stratified by Prior Docetaxel Use




**Reference:** Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

# ALSYMPCA: Time to First SRE




| | Radium-223 dichloride (n = 614) | Placebo (n = 307) |
|---|---|---|
| Median time to SRE (months) | 12.2 | 6.7 |
| Hazard ratio | 0.64 | |
| 95% CI | 0.52–0.78 | |
| *P* value | <0.0001 | |

**Reference:** Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

# ALSYMPCA: Time to First SRE Components

| | N (%) of Events | | Time to Event (Radium-223 dichloride vs. Placebo) | |
|---|---|---|---|---|
| **SRE Component** | **Radium-223 dichloride (n = 614)** | **Placebo (n = 307)** | ***P* value** | **HR (95% CI)** |
| **External-beam radiotherapy** | 186 (30.3) | 105 (34.2) | 0.00117 | 0.67 (0.52-0.85) |
| **Spinal cord compression** | 25 (4.1) | 21 (6.8) | 0.025 | 0.51 (0.28-0.93) |
| **Pathologic bone fracture** | 32 (5.2) | 20 (6.5) | 0.09 | 0.62 (0.35-1.09) |
| **Surgical intervention** | 12 (2) | 7 (2.3) | 0.479 | 0.71 (0.28-1.8) |

**Reference:** Sartor et al. *J Clin Oncol.* 2012;30 (suppl): abstract 4551. Presented at ASCO 2012.

# ALSYMPCA: Overall Safety Data

**Patients with adverse events (AEs), n (%)**

| | Radium-223 dichloride (n = 600) | Placebo (n = 301) |
|---|---|---|
| All AEs | 558 (93) | 290 (96) |
| Grade 3 or 4 AEs | 349 (58) | 197 (66) |
| Serious AEs (SAEs) | 281 (47) | 181 (60) |
| Discontinuation due to AEs | 99 (17) | 62 (21) |
| Deaths due to AEs | 96 (16) | 67 (23) |

**Reference:** Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

# ALSYMPCA: Median Number of Injections

| | Radium-223 dichloride (n = 614) | Placebo (n = 307) |
|---|---|---|
| Patients treated, n | 599 | 302 |
| Median number of injections, range | 6 (1-6) | 5 (1-6) |
| Received all 6 injections, n (%) | 387 (63) | 145 (47) |

ITT group (n = 921)

**Reference:** Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

# ALSYMPCA: Adverse Events of Interest

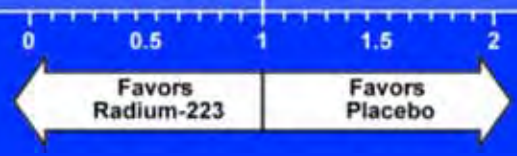
**Patients with AEs, n (%)**

| | All Grades | | Grades 3 or 4 | |
|---|---|---|---|---|
| | **Radium-223 dichloride (n = 600)** | **Placebo (n = 301)** | **Radium-223 dichloride (n = 600)** | **Placebo (n = 301)** |
| Hematologic | | | | |
| Anemia | 187 (31.2) | 92 (31) | **77 (13)** | **40(13)** |
| Neutropenia | 30 (5) | 3 (1) | **13 (2)** | **2 (1)** |
| Thrombocytopenia | 69 (11.5) | 17 (5.6) | **39 (6.5)** | **6 (2)** |
| Non-hematologic | | | | |
| Bone pain | 300 (50) | 187 (62) | **125 (21)** | **77 (26)** |
| Diarrhea | 151 (25) | 45 (15) | **9 (1.5)** | **5 (1.7)** |
| Nausea | 213 (35.5) | 104 (35) | **10 (2)** | **5 (2)** |
| Vomiting | 111 (18.5) | 41 (14) | **10 (2)** | **7 (2)** |
| Constipation | 108 (18) | 64 (21) | **6 (1)** | **4 (1)** |

**Reference:** Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

# ALSYMPCA: Survival Benefit Across Patient Subgroups

| Variable | Subgroup | N | HR | 95% CI |
|---|---|---|---|---|
| Overall Survival | | 921 | 0.695 | 0.581–0.832 |
| Total ALP # | < 220 U/L | 517 | 0.825 | 0.635–1.072 |
| | ≥ 220 U/L | 404 | 0.619 | 0.486–0.788 |
| Current Use of Bisphosphonates # | Yes | 374 | 0.699 | 0.525–0.931 |
| | No | 547 | 0.736 | 0.587–0.923 |
| Prior Use of Docetaxel # | Yes | 526 | 0.710 | 0.565–0.891 |
| | No | 395 | 0.745 | 0.562–0.987 |
| Baseline ECOG Status | 0 or 1 | 801 | 0.675 | 0.555–0.821 |
| | 2 or Higher | 118 | 0.820 | 0.498–1.351 |




**Reference:** Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

# Chemotherapy Post-Radium-223 Dichloride Treatment Subgroup Analysis

# Patients Treated with Chemotherapy After Radium-223 Dichloride*

The proportion of patients receiving chemotherapy following ALSYMPCA

- 90 out of 615 patients (15%) in the radium-223 dichloride group
- 54 out of 307 patients (18%) in the placebo group

The most common chemotherapeutic agents administered after study drug treatment were docetaxel (n = 105), mitoxantrone (n = 23), and cyclophosphamide (n = 19)

*Post-hoc analysis

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

# Patient Demographics and Baseline Characteristics*

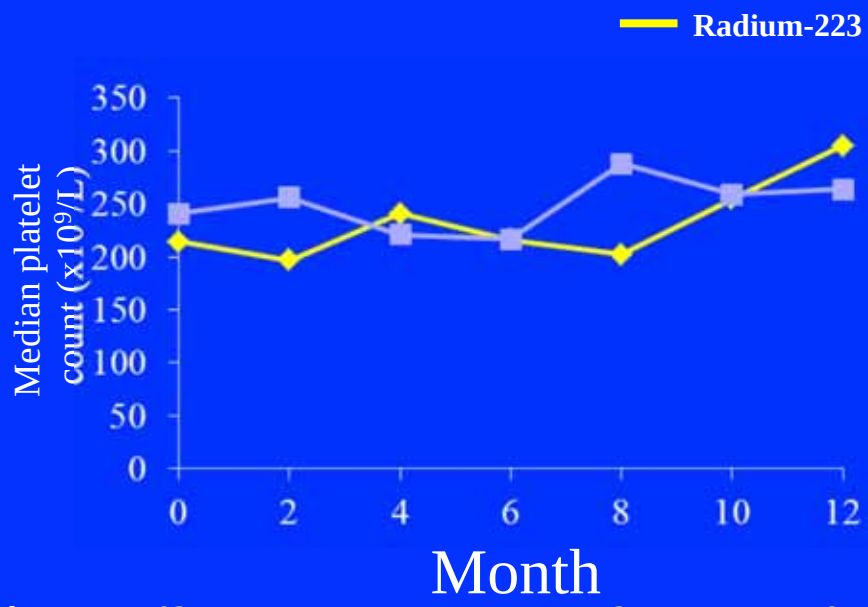
| | Radium-223 (n = 93) | Placebo (n = 54) |
|---|---|---|
| Mean age, years | 67.2 | 68.2 |
| Caucasian race, n (%) | 86 (93) | 50 (93) |
| Baseline ECOG PS, n (%)<br>≤ 1<br>2 | <br>88 (95)<br>5 (5) | <br>47 (87)<br>7 (13) |
| WHO ladder, cancer pain index, ≥ 2, n (%) | 48 (52) | 29 (54) |
| Total ALP, n (%)<br>< 220 U/L<br>≥ 220 U/L | <br>59 (63)<br>34 (37) | <br>38 (70)<br>16 (30) |
| Current use of bisphosphonates, n (%)<br>Yes<br>No | <br>45 (48)<br>48 (52) | <br>24 (44)<br>30 (56) |
| Median number of study drug injections, range | 6 (2–6) | 5.5 (1–6) |
| Patients receiving all 6 injections of study drug, n (%) | 66 (71) | 27 (50) |
| Any prior use of docetaxel, n (%)<br>Yes<br>No | <br>63 (68)<br>30 (32) | <br>32 (59)<br>22 (41) |

ALP = alkaline phosphatase; ECOG = Eastern Cooperative Oncology Group *Post-hoc analysis

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

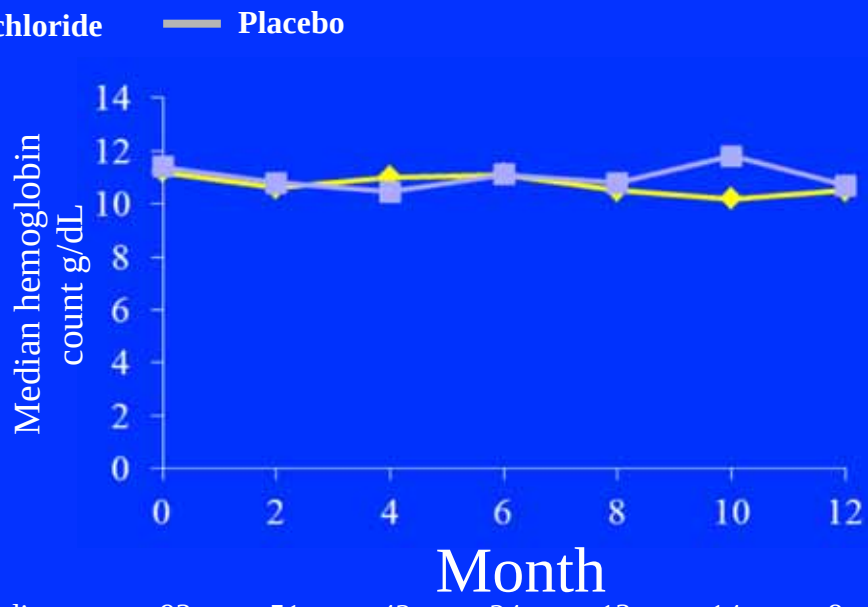
# Cytotoxic Chemotherapy Following ALSYMPCA Participation: Safety*

**Platelets**




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Radium, n | 93 | 51 | 42 | 24 | 13 | 14 | 8 |
| Placebo, n | 54 | 34 | 20 | 14 | 7 | 9 | 6 |

**Hemoglobin**



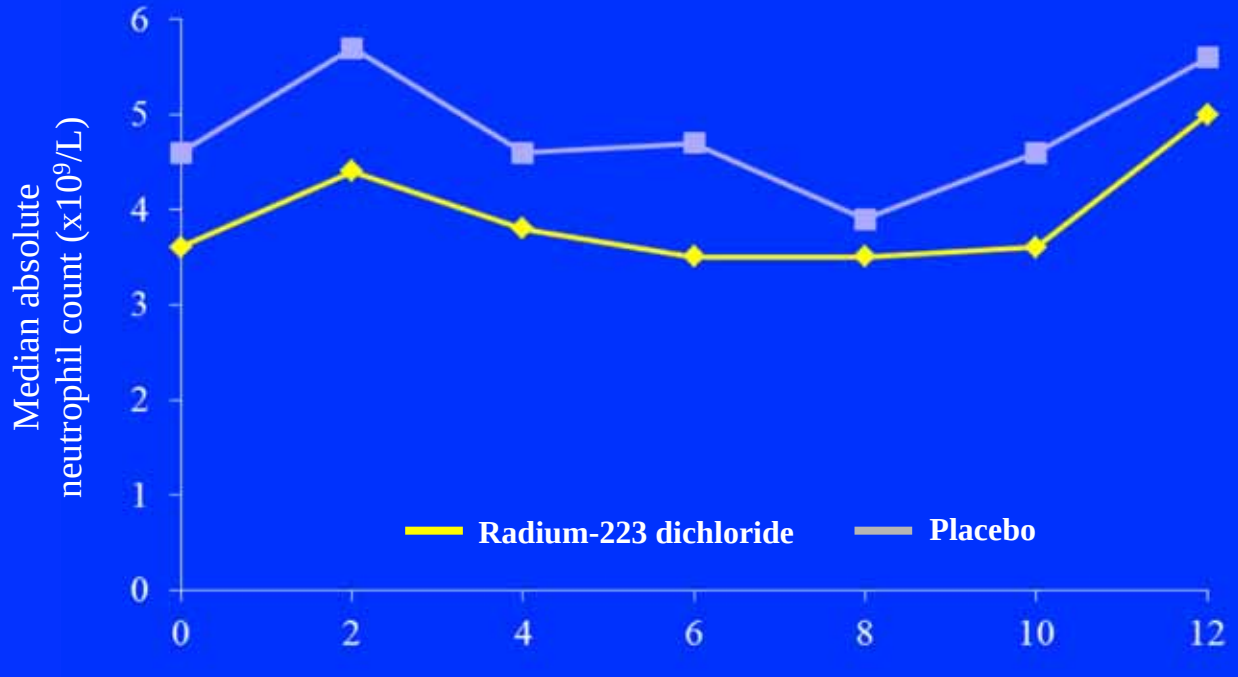

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Radium, n | 93 | 51 | 42 | 24 | 13 | 14 | 8 |
| Placebo, n | 54 | 34 | 20 | 14 | 7 | 9 | 6 |

*Post-hoc analysis

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

# Cytotoxic Chemotherapy Following ALSYMPCA Participation: Safety*

**Neutrophils**




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Radium, n | 91 | 47 | 42 | 23 | 12 | 13 | 8 |
| Placebo, n | 49 | 30 | 19 | 12 | 7 | 8 | 6 |

*Post-hoc analysis

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


RANDOMIZATION
1:1:1
GROUP 1, n = 22
Radium-223 50 kBq/kg IV every 4 wk × 6
GROUP 2, n = 22
Radium-223 50 kBq/kg IV every 4 wk × 6
Abiraterone 1000 mg qd PO and prednisone 5 mg bid × 2 y following last radium-223 dose
GROUP 3, n = 22
Radium-223 50 kBq/kg IV every 4 wk × 6
Enzalutamide 160 mg qd PO × 2 y following last radium-223 dose

# Rad 223 + Docetaxel
# Abstract 5021

- Cohort 1: Rad 223 25 kbq/kg x q 6 weeks x 2 + docetaxel 75 mg/m2 (7 pts)
- Cohort 2 Rad 223  25 kbq/kg q 6 week x2 + docetaxel 60 mg/m2  (3 pts)
- Cohort 3 Rad 223  50 kbq/kg q 6 week x2 + docetaxel 60 mg/m2  (7 pts)

# Rad 223 + Docetaxel
# Abstract 5021

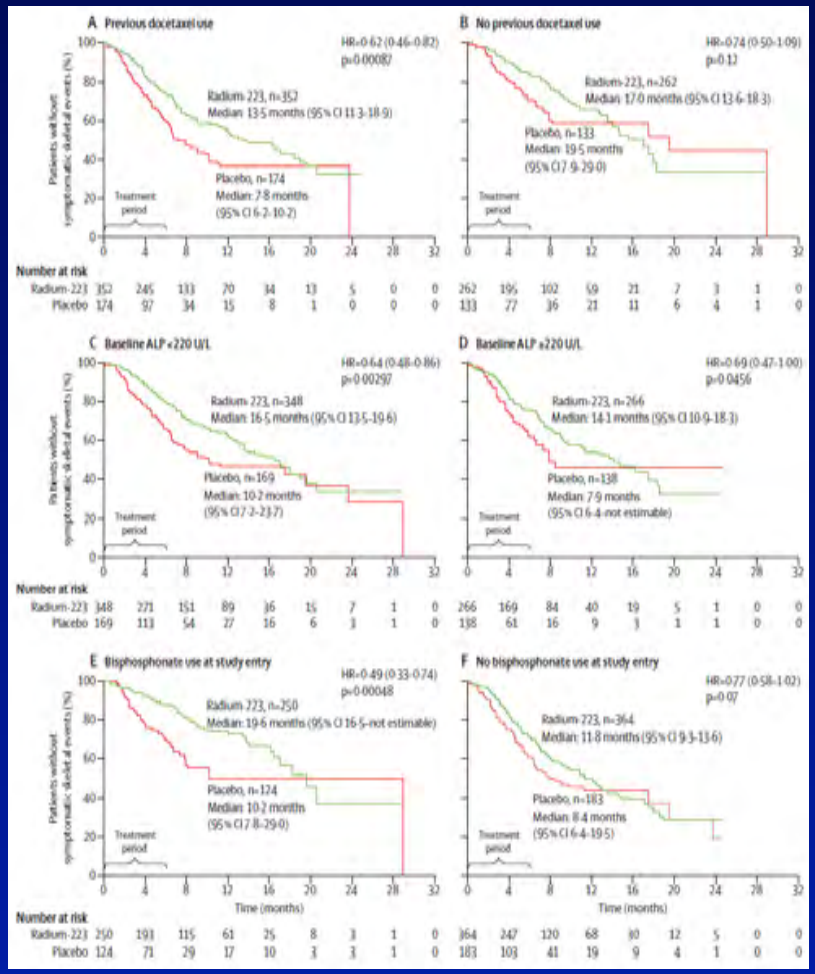
- No discontinuation or delay of Rad 223 due to protocol defined AE's
- No grade 3/4 anemia or thrombocytopenia
- 10 patients had grade 3/4 neutropenia
- 4 cases of febrile neutropenia
  - Cohort 1 3 pts
  - Corhort 3  1 patient

# Rad 223 + Docetaxel
# Abstract 5021

- Proceeding to  a randomized phase II cohort of Rad 223 50 kbq/kg q 6 weeks x 5 + docetaxel 60 mg/m2

# Sartor et al: Effect of Radium 223 dichloride on Symptomatic Skelatal Events(SSE) in Patients with CRPC and Bone Metastases

- SSE occurred in 33% of the 614 patients treated with Radium 223 vs 38% of 307 patients in the placebo group
- Time to first SSE was longer in Radium 223 patient (15.6 months) vs placbo (9.8 months)



# Sartor et al: Effect of Radium 223 dichloride on Symptomatic Skelatal events in Patients with CRPC and Bone Metastases

- Of the individual components of SSEs, a significant reduction was noted in Radium 223 patients in the need for external beam radiation therapy (30% v 34%, p=0.00117) and the incidence of spinal cord compression (4% vs 7%, p=0.03)
- No difference was noted in the rate of symptomatic pathological bone fractures or tumor relates orthopedic surgical events.

# Nilssson et al : 1.5 year Posttreatment Follow-up of Radium 223 Dichloride in Patients with Castration Resistant Prostate Cancer and Bone Metastases form Phase 3 ALSYMCA Study

- 921 patients randomized, 574 entered 3 year follow-up (Radium 223= 406, placebo=168)
- Of the patient on the Radium 223 arm, 335(83%) received all 6 study treatment injections.
- 65% and 59% of patients on the Rad 223 and placebo arms, respectively died during the follow-up period.
- Incidence of myelosupression among radium was low (<3%) in patients treated with radium 223
- No reports of acute myelogenous leukemia (AML), myleodysplastic syndrome ( MDS), or primary bone cancer.
- No additional safety issues identified.

# Conclusions

- Alpha emitting isotope therapy improves survival in men with castration resistant prostate cancer
- Minimal toxicity
- Combination studies with hormonal/ chemotherpeutic agents are undeway