La enfermedad ósea en el cáncer de próstata | Bone disease in prostate cancer

Dr. Dominik Berthold
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OUTLINE

1. Osteoposis: definition
2. Impact of Androgen Deprivation Therapy (ADT) in men with prostate cancer (PCa)
3. Bone mets in prostate cancer
4. Drugs acting on bone metabolism in PCa patients: biphosphonate and RANK-L antagonists
5. Radium-223
6. Radiotherapy/Imaging
7. Take home messages
8. Cases
Case discussion RG 1942

1996: Radical prostatectomy, pT3a pN0 M0, GI 6

2002: biochemical relapse: salvage radiation complicated by radiation-induced cystitis=> since 2008 permanent bladder catheter

2010; rising PSA, pelvic mass, no Bone mets => start of ADT

2012: bone metastasis, CRPC

Comorbidities:
- Crohn disease
- Moderate renal insufficiency
- Diabetes type II, requiring insulin
- Osteoporotic vertebral fracture in 2007, treated with vertebroplasty, calcium/vit D, ibandronate
What would you have done?

1. Start on docetaxel
2. Supplement with calcium/vit D
3. Consider denosumab instead of ibandronate
4. Consider radiation to painful bone metastasis
5. All of the above
The patient had **Docetaxel** x4 (with radiological response, but significant side effects)

Switch to **Denosumab** 120mg q1m

⇒ After 4 months develops **ONJ**

At progression after docetaxel:

⇒ enzalutamide:

⇒ response for almost 2 years

At progression he presents with painful bone metastasis

2.2014: What are his options now?

1. Abiraterone
2. Radium-223
3. Re-start denosumab
4. Start zolendronate
5. Consider local treatment (radiation, vertebroplasty)
SREs and treatments

Vertebroplasty
Radiation to bone
Bicalutamide
Docetaxel
Ibandronate
Densoumab
Castration
Calcium/Vitamin D

2012
2013
2014

ONJ
Vertebroplasty
Hip fracture
Radiation to bone
Radium 223
Abiraterone
OSTEOPOROSIS DEFINITION

It is characterized by bone frailty due to bone mass decrease and alteration of bone architecture.

Bone density results from an equilibrium between osteoblastic and osteoclastic activity.

Osteoporosis is due to an excess of osteoclasts.

Factors favoring osteoporosis are:
- Genetic
- Nutritional (vitamine D and calcium)
- Environmental (smoking+++ , sun exposure…)
- Ageing

40% of patients older than 70 have Vitamin D deficit.
Osteoporosis

Normal bone

Severe osteoporosis

Osteoporosis

Courtesy JP Droz
Consequences of osteoporosis = fractures

Fracture of the wrist  Vertebral fracture  Fracture of the hip

Courtesy JP Droz
Consequence: handicap

Courtesy JP Droz
measure ⇒ ostéodensitometry
Depletion of testosterone and oestrogen accelerates bone resorption by osteoclasts

Depletion of testosterone and oestrogen accelerates bone resorption by osteoclasts.

Androgen

Oestrogen

Decreased osteoblast activity

Increased osteoclast activity

Increased bone resorption

Osteoblasts (bone formation)

Osteoclast (bone resorption)

Published series consistently show decreased bone mineral density after one year of ADT.

- **Total hip**
  - Morote et al: -3.7
  - Smith et al: -3.3
  - Berruti et al: -3.0
  - Mittan et al: -2.7
  - Smith et al: -2.3

- **Femoral neck**
  - Daniell et al: -3.9
  - Maillefer et al: -4.6

- **Lumbar spine**
  - Maillefer et al: -4.8

ADT is associated with rapid and clinically significant bone loss

Naturally-occurring bone loss

- Normal men: 0.5%
- Postmenopausal women > 55 yrs: 1.0%
- Menopausal women < 55 yrs: 2.0%
- AI therapy in postmenopausal women: 2.6%

Cancer treatment-induced bone loss

- ADT³: 4.6%
- AI therapy + GnRH agonist in premenopausal women: 7.4%
- Premature menopause secondary to chemotherapy: 7.7%

ADT increases risk of fracture

Fractures and post-fracture mortality in prostate cancer patients receiving ADT

- Analysis from SEER database
- n=72,400 pts with prostate cancer diagnosed 1996–2003

<table>
<thead>
<tr>
<th></th>
<th>Orchidectomy</th>
<th>LHRH-agonist during first 6 months after diagnosis</th>
<th>No ADT during follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent patients</td>
<td>2.2</td>
<td>47.2</td>
<td>50.6</td>
</tr>
<tr>
<td>Fracture risk, HR (95% CI)</td>
<td>1.7 (1.5–1.9)</td>
<td>1.3 (1.3–1.4)</td>
<td>1</td>
</tr>
<tr>
<td>Fractures resulting in hospitalisation, HR (95% CI)</td>
<td>1.9 (1.6–2.3)</td>
<td>1.4 (1.3–1.5)</td>
<td>1</td>
</tr>
</tbody>
</table>

- Fractures resulting in hospitalisation were associated with increased mortality (HR, 1.2; 95% CI, 1.2–1.3)

Fractures increase mortality

Multivariate forward stepwise regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value</th>
<th>Relative death risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal metastasis</td>
<td>0.002</td>
<td>9.5 (8.5–10.5)</td>
</tr>
<tr>
<td>Skeletal fracture history</td>
<td>0.007</td>
<td>7.4 (6.1–8.7)</td>
</tr>
<tr>
<td>Nadir PSA</td>
<td>0.09</td>
<td>2.8 (0.8–4.8)</td>
</tr>
</tbody>
</table>

**Options to help reduce bone loss**

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADT modification</strong></td>
<td><strong>Bone resorption agents</strong></td>
</tr>
<tr>
<td>• Minimise duration</td>
<td>• Bisphosphonates</td>
</tr>
<tr>
<td>• Deferred vs early</td>
<td>• Denosumab</td>
</tr>
<tr>
<td>• Intermittent administration</td>
<td></td>
</tr>
<tr>
<td>• Alternative forms</td>
<td></td>
</tr>
<tr>
<td>e.g. bicalutamide monotherapy</td>
<td></td>
</tr>
<tr>
<td><strong>Lifestyle changes</strong></td>
<td></td>
</tr>
<tr>
<td>• Diet and exercise</td>
<td></td>
</tr>
<tr>
<td>• Calcium and vitamin D supplements</td>
<td></td>
</tr>
<tr>
<td>• Avoid alcohol and smoking</td>
<td></td>
</tr>
</tbody>
</table>
Effect of bisphosphonates on bone mineral density in men with prostate cancer

- Zoledronate 4 mg IV /12 months (n=106)
  - Total hip
  - Lumbar spine

- Zoledronate 4 mg IV /3 months (n=40)
  - Total hip
  - Lumbar spine

- Alendronate 70 mg Oral /weekly (n=112)
  - Total hip
  - Lumbar spine

Change in BMD (%) after 1 year

Denosumab inhibits RANK Ligand

Denosumab

- Fully human monoclonal antibody
- Precisely binds to RANK Ligand
  - Inhibits the formation, function and survival of osteoclasts
  - ↓ bone resorption

Osteoblasts

Denosumab is investigational and not approved anywhere in the world
Denosumab significantly increased BMD at 24 months vs placebo

- Increase in BMD with denosumab was rapid
- Increase in BMD was significant at all measured sites (P ≤ 0.001)

Denosumab significantly reduced incidence of new vertebral fractures

- Month 12: Placebo (n=673) 1.9%, Denosumab (n=679) 0.3%
  - Reduction: 85%
  - P=0.004

- Month 24: Placebo (n=673) 3.3%, Denosumab (n=679) 1.0%
  - Reduction: 69%
  - P=0.004

- Month 36: Placebo (n=673) 3.9%, Denosumab (n=679) 1.5%
  - Reduction: 62%
  - P=0.006

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FRAX®
WHO Fracture Risk Assessment Tool

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: Austria  
Name/ID: JMR  
About the risk factors

Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: 73  
   Date of birth: Y: 1937 M: 11 D: 12

2. Sex
   Male  Female

3. Weight (kg)
   79

4. Height (cm)
   168

5. Previous fracture
   No  Yes

6. Parent fractured hip
   No  Yes

7. Current smoking
   No  Yes

8. Glucocorticoids
   No  Yes

9. Rheumatoid arthritis
   No  Yes

10. Secondary osteoporosis
    No  Yes

11. Alcohol 3 or more units per day
    No  Yes

12. Femoral neck BMD (g/cm²)
    T-Score: 2.4

BMI 28.0
The ten year probability of fracture (%)
with BMC
- Major osteoporotic: 18
- Hip fracture: 11

ADT

Treatment recommended if:
- Hip fracture >3%
- Major osteoporotic fracture >20%
Question 1

A man with locally advanced PC will be treated with RT and ADT for 3 years. Choose the following best answer:

1. Treat with Denosumab 120 mg and vit D
2. Treat with Zoledronic Acid and Vit D
3. Recommend vit D and calcium, evaluate risk for osteoporosis
4. Withhold ADT until progression
5. All the answers are right
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3. Bone mets in prostate cancer
4. Drugs acting on bone metabolism in PCa patients: biphosphonate and RANK-L antagonists
5. Indications in PCa patients: prevention of osteoporosis
6. Indications in PCa patients: delay in bone mets progression, impact on bone events occurrence
7. Radium-223
8. Radiotherapy/Imaging
9. Take home messages
10. Cases
Bone metastases are the most prevalent metastasis in CRPC


Epidemiological data from docetaxel trials.
MECHANISMS OF BONE METS

The Batson plexus.
Model “Seed and Soil” (Paget 1889)
COMPLICATIONS of BONE MTS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>50-90%</td>
</tr>
<tr>
<td>Fractures</td>
<td>30%</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>10%</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>10%</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>
Bone Cancer
Primary Bone Cancers and Bone Metastases

Edited by
Dominique Heymann
Interaction of tumor cells and Nociceptor
Prostate cancer cells sprouting of sensitory nerve fibers in bone
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Bisphosphonate Pharmacology

**Proposed mode of action**

- Aminobisphosphonates
- Mature osteoclasts
- Accession
- Prostaglandins and other factors
- Tumour cells
- Bone
- Bony Complications
- Bisphosphonates

- Precursor cells
Bisphosphonates

Binding to Apatite Crystals

Preferential Accumulation under Osteoclasts

Local Release during Bone Resorption

Osteoclast Apoptosis

Osteoclast Activity

Osteoblast Recruitment
Bone remodelling can become deregulated in the presence of tumour cells. A vicious cycle of bone destruction and tumour growth may develop.
Denosumab binds human RANK Ligand to inhibit osteoclast formation, function and survival

Bone metastases can have serious and debilitating consequences – skeletal-related events (SREs)

- SREs are defined as:
  - Radiation to bone
  - Pathological fracture
  - Spinal cord compression
  - Surgery to bone

Prior SRE increases the risk for subsequent SRE

- Kaminski M, et al. Poster presented at ASCO 2004 (Abstract 857);

SREs can have serious consequences

- Bone metastases in prostate cancer
- Increased pain
- Increased mortality

Cost of SREs
- Decreased mobility
- Increased hospitalisation rate and duration
- Decreased quality of life
Zoledronic acid is the only bisphosphonate proven to reduce risk of SREs in men with CRPC and bone metastases.

Proportion of patients with ≥ 1 SRE

- Zoledronic acid 4 mg (n = 214): 33.2%
- Zoledronic acid 8/4 mg (n = 221): 38.5%
- Placebo (n = 208): 44.2%

Time to first SRE

- Zoledronic acid 4 mg (P = 0.011 vs placebo)
- Zoledronic acid 8/4 mg (P = 0.491 vs placebo)
- Placebo

Pivotal head-to-head studies of denosumab vs zoledronic acid for SRE prevention

Breast cancer (N = 2046)

Prostate cancer (N = 1901)

Other solid tumours* (N = 1776)

RANDOMISATION

Prespecified integrated analysis (N = 5723)

Denosumab 120 mg SC and placebo IV every 4 weeks (n = 2862)

Supplemental calcium and vitamin D

Zoledronic acid 4 mg IV and placebo SC every 4 weeks (n = 2861)

*Excluding breast or prostate.
Phase III study of denosumab vs zoledronic acid in CRPC patients with bone metastases

**Inclusion criteria**
- CRPC
- Bone metastases

**Exclusion criteria**
- Oral bisphosphonates for the treatment of bone metastases
- Prior IV bisphosphonates

**Study 103**

Enrolled N = 1904

Randomisation

- **Denosumab** 120 mg SC Q4W + Placebo IV Q4W* (n = 950)
  - Daily supplementation with calcium (≥ 500 mg) and vitamin D (≥ 400 IU)

- **Zoledronic acid** 4 mg IV Q4W* + Placebo SC Q4W (n = 951)

*Per protocol and Zometa® label, IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine.

Significantly longer time without an SRE with denosumab vs zoledronic acid

Time to first SRE

18% Risk Reduction

HR = 0.82 (95% CI, 0.71–0.95)
P = 0.008 (superiority)

(n = 1901)


HR, hazard ratio.
Exploratory Endpoint: Overall Survival

HR = 1.03 (95% CI, 0.91–1.17)

$P = 0.65$

## Summary of Adverse Events

<table>
<thead>
<tr>
<th>Patient Incidence</th>
<th>Denosumab (N = 943) n (%)</th>
<th>Zoledronic Acid (N = 945) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event (AE)</td>
<td>916 (97)</td>
<td>918 (97)</td>
</tr>
<tr>
<td>Most Common AEs in Either Arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>337 (36)</td>
<td>341 (36)</td>
</tr>
<tr>
<td>Back pain</td>
<td>304 (32)</td>
<td>287 (30)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>267 (28)</td>
<td>274 (29)</td>
</tr>
<tr>
<td>Nausea</td>
<td>272 (29)</td>
<td>245 (26)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>257 (27)</td>
<td>222 (23)</td>
</tr>
<tr>
<td>CTCAE grade 3 or 4 AEs</td>
<td>678 (72)</td>
<td>628 (66)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>594 (63)</td>
<td>568 (60)</td>
</tr>
<tr>
<td>AEs leading to treatment discontinuation</td>
<td>164 (17)</td>
<td>138 (15)</td>
</tr>
</tbody>
</table>

Hypocalcaemia occurred more frequently in the denosumab arm vs the zoledronic acid arm (121 [13%] vs 55 [6%]).

CTCAE = Common Terminology Criteria for Adverse Events.

## Adverse Events of Interest

<table>
<thead>
<tr>
<th>Subject incidence, n (%)</th>
<th>Zoledronic Acid (N = 945)</th>
<th>Denosumab (N = 943)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious AEs</td>
<td>375 (39.7)</td>
<td>402 (42.6)</td>
</tr>
<tr>
<td>Infectious serious AEs</td>
<td>108 (11.4)</td>
<td>130 (13.8)</td>
</tr>
<tr>
<td><strong>Acute phase reactions (first 3 days)</strong></td>
<td>168 (17.8)</td>
<td>79 (8.4)</td>
</tr>
<tr>
<td>Renal AEs*</td>
<td>153 (16.2)</td>
<td>139 (14.7)</td>
</tr>
<tr>
<td>Cumulative rate of osteonecrosis of the jaw (ONJ)†</td>
<td>12 (1.3)</td>
<td>22 (2.3)</td>
</tr>
<tr>
<td>Year 1</td>
<td>5 (0.5)</td>
<td>10 (1.1)</td>
</tr>
<tr>
<td>Year 2</td>
<td>8 (0.8)</td>
<td>22 (2.3)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Calcium and Vitamin D3 strongly recommended!</td>
<td></td>
</tr>
<tr>
<td>New primary malignancy</td>
<td>10 (1.1)</td>
<td>18 (1.9)</td>
</tr>
</tbody>
</table>

*Includes renal failure, increased blood creatinine, acute renal failure, renal impairment, increased blood urea, chronic renal failure, oliguria, hypercreatininemia, anuria, azotemia, decreased creatinine renal clearance, decreased urine output, abnormal blood creatinine, proteinuria, decreased glomerular filtration rate, and nephritis.

†*P = 0.09
Question 2

- This is a men with newly diagnosed metastatic prostate cancer to bone. He will be treated with degarelix. Consider also:

1. bicalutamide to prevent bone pain
2. determination of calcium and vit D
3. denosumab 120mg every month
4. radium 223
5. calcium/vit D supplements
An important side effect of bisphosphonates and Denosumab: osteonecrosis of the jaw

Incidence increases with time and infusion number
Favored by drugs (corticoids, antiangiogenic), gengival trauma or surgery
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radium-223 is an α-particle emitting radiopharmaceutical approved for patients with metastatic castration resistant prostate cancer*

- Radium belongs to the same group of elements as Calcium
- Radium is a calcium-mimetic element
- Radium (Ra-223) is quickly taken up in newly forming bone
Radium-223 is a calcium mimetic and an alpha emitter

Radium-223 is incorporated into the bone mineral hydroxyapatite in areas of increased bone turnover\textsuperscript{1,2}

High LET of alpha emitters leads to a high frequency of double-strand DNA breaks in adjacent tumour cells, resulting in a local antitumour effect\textsuperscript{3}

Drawings are not to scale. LET = Linear energy transfer.

Decay of Radium-223 Dichloride

- $t_{1/2} = 11.4$ days\(^1\)
- The six-stage-decay of radium-223 to lead-207 occurs via short-lived daughters, and is accompanied by a number of alpha, beta and gamma emissions with different energies and emission probabilities\(^1\)
- Of the total decay energy\(^2\)
  - 95.3% emitted as $\alpha$-particles
  - 3.6% emitted as $\beta$-particles
  - 1.1% emitted as $\gamma$- or X-rays

The gamma radiation associated with the decay of radium-223 allows radioactivity measurement of drug product and the detection of contaminations with standard instruments\(^1\)

\(^1\) Xofigo Professional Information, Status August 2014, www.swissmedicinfo.ch
Alpha Emitter Versus Beta Emitter

**Alpha Emitter**

- Short range of alpha emitters (5-10 cell diameters or 40-100 μm)
- Radium-223
- Bone marrow
- Bone

**Beta Emitter**

- Long range of beta emitters (0.2-12 mm)
- Bone marrow
- Bone
- β emitter

ALSYMPCA: Study Design

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

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

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

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.

ALSYMPCA: Endpoints

**PRIMARY ENDPOINT**
- Overall survival

**MAIN SECONDARY ENDPOINTS**
- Time to occurrence of first SSE
- Time to total ALP progression
- Total ALP response
- Total ALP normalization\(^a\)
- Time to PSA progression\(^b\)
- Safety
- Quality of life

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

\(a\). 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.

\(b\). 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.

the time to the first symptomatic skeletal event was defined as any of the following:

- the first use of external-beam radiation therapy to relieve skeletal symptoms
- new symptomatic pathologic vertebral or nonvertebral bone fractures
- spinal cord compression
- tumor-related orthopedic surgical intervention

Whereas other trials included asymptomatic fractures—detected by means of periodic radiologic review—as skeletal events, ALSYMPCA had no radiographic review and so only symptomatic pathologic bone fractures were captured. Thus “symptomatic skeletal event” (SSE) was deemed a more clinically relevant term for this measurement.
## ALSYMPCA: Patient Demographics and Baseline Characteristics (ITT Population)

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>RADIUM-223 (n=614)</th>
<th>PLACEBO (n=307)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, Median (range)</td>
<td>71 (49-90)</td>
<td>71 (44-94)</td>
</tr>
<tr>
<td>&gt;75 years, n (%)</td>
<td>171 (28)</td>
<td>90 (29)</td>
</tr>
<tr>
<td>Caucasian race, n (%)</td>
<td>575 (94)</td>
<td>290 (94)</td>
</tr>
<tr>
<td>Total ALP, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;220 U/L</td>
<td>348 (57)</td>
<td>169 (55)</td>
</tr>
<tr>
<td>≥220 U/L</td>
<td>266 (43)</td>
<td>138 (45)</td>
</tr>
<tr>
<td>Current use of bisphosphonates, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>250 (41)</td>
<td>124 (40)</td>
</tr>
<tr>
<td>No</td>
<td>364 (59)</td>
<td>183 (60)</td>
</tr>
<tr>
<td>Any prior use of docetaxel, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>352 (57)</td>
<td>174 (57)</td>
</tr>
<tr>
<td>No</td>
<td>262 (43)</td>
<td>133 (43)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td>165 (27)</td>
<td>78 (25)</td>
</tr>
<tr>
<td>0</td>
<td>371 (60)</td>
<td>187 (61)</td>
</tr>
<tr>
<td>≥2</td>
<td>77 (13)</td>
<td>41 (13)</td>
</tr>
</tbody>
</table>

ALP, alkaline phosphatase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intention-to-treat.

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>RADIUM-223 (n=614)</th>
<th>PLACEBO (n=307)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO ladder for cancer pain, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>257 (42)</td>
<td>137 (45)</td>
</tr>
<tr>
<td>2</td>
<td>151 (25)</td>
<td>78 (25)</td>
</tr>
<tr>
<td>3</td>
<td>194 (32)</td>
<td>90 (29)</td>
</tr>
<tr>
<td>Extent of disease, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 metastases</td>
<td>100 (16)</td>
<td>38 (12)</td>
</tr>
<tr>
<td>6-20 metastases</td>
<td>262 (43)</td>
<td>147 (48)</td>
</tr>
<tr>
<td>&gt;20 metastases</td>
<td>195 (32)</td>
<td>91 (30)</td>
</tr>
<tr>
<td>Superscan</td>
<td>54 (9)</td>
<td>30 (10)</td>
</tr>
<tr>
<td>EBRT within 12 weeks of screening, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>99 (16)</td>
<td>48 (16)</td>
</tr>
<tr>
<td>No</td>
<td>515 (84)</td>
<td>259 (84)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL), Median (range)</td>
<td>12.2 (8.5-15.7)</td>
<td>12.1 (8.5-16.4)</td>
</tr>
<tr>
<td>Albumin (g/L), Median (range)</td>
<td>40 (24-53)</td>
<td>40 (23-50)</td>
</tr>
<tr>
<td>Total ALP (U/L), Median (range)</td>
<td>211 (32-6431)</td>
<td>223 (29-4805)</td>
</tr>
<tr>
<td>LDH (U/L), Median (range)</td>
<td>315 (76-2171)</td>
<td>336 (132-3856)</td>
</tr>
<tr>
<td>PSA (µg/L), Median (range)</td>
<td>146 (3.8-6026)</td>
<td>173 (1.5-14500)</td>
</tr>
</tbody>
</table>

ITT, intention-to-treat; WHO, World Health Organization.

The updated analysis confirmed the interim analysis 30% reduction in risk of death for patients in the radium-223 group compared with placebo.

## ALSYMPCA: Overall Survival Across Patient Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of Patients</th>
<th>Median Overall Survival (months)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radium-223</td>
<td>Placebo</td>
<td>Radium-223</td>
</tr>
<tr>
<td>All patients</td>
<td>614</td>
<td>307</td>
<td>14.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ALP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;220 U/L</td>
<td>348</td>
<td>169</td>
<td>17.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥220 U/L</td>
<td>266</td>
<td>138</td>
<td>11.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use of bisphosphonates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>250</td>
<td>124</td>
<td>15.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>364</td>
<td>183</td>
<td>14.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior use of docetaxel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>352</td>
<td>174</td>
<td>14.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>262</td>
<td>133</td>
<td>16.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline ECOG PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>536</td>
<td>265</td>
<td>15.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>77</td>
<td>41</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 Metastases</td>
<td>100</td>
<td>38</td>
<td>27.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-20 Metastases</td>
<td>262</td>
<td>147</td>
<td>13.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20 Metastases</td>
<td>195</td>
<td>91</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superscan</td>
<td>54</td>
<td>30</td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>345</td>
<td>168</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No&lt;sup&gt;b&lt;/sup&gt;</td>
<td>269</td>
<td>139</td>
<td>16.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ECOG=Eastern Cooperative Oncology Group; NE=not evaluated; PS=performance status.

<sup>a</sup>Patients with a score of 2 or 3 on the World Health Organization (WHO) ladder for cancer pain.

<sup>b</sup>Patients without pain or opioid use at baseline and patients with a score of 1 on the WHO ladder for cancer pain.

ALSYMPCA: Overall Survival and Docetaxel Use

Chemo-naive
(43% of patients)

4.6 months’ increase

HR=0.75; 95% CI: 0.56-0.99

\( P=0.039 \)

Prior Docetaxel Use
(57% of patients)

3.1 months’ increase

HR=0.71; 95% CI: 0.56-0.89

\( P=0.003 \)

*BSoC (Best standard of care) included local external-beam radiation therapy or treatment with glucocorticoids, antiandrogens, ketoconazole, or estrogens such as diethylstilbestrol or estramustine.

ALSYMPCA: Median Time to First SSE (Updated Analysis)

5.8 Months of median delay
HR (95% CI) = 0.66 (0.52-0.83)
P<0.001

Radium-223 + BSoC\(^a\) (n=614); median time to first SSE, 15.6 months
Placebo + BSoC\(^a\) (n=307); median time to first SSE, 9.8 months

\(^a\)BSoC (Best standard of care) included local external-beam radiation therapy or treatment with glucocorticoids, antiandrogens, ketoconazole, or estrogens such as diethylstilbestrol or estramustine.

**ALSYMPCA: Kaplan–Meier estimates of time to first SSE by baseline stratification factor: Bisphosphonate Use at Study Entry (Yes/No)**

<table>
<thead>
<tr>
<th>BISPHOSPHONATE USE AT STUDY ENTRY</th>
<th>NO BISPHOSPHONATE USE AT STUDY ENTRY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
<td>Patients Without Symptomatic Skeletal Events, %</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
</tr>
<tr>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>32</td>
<td>0</td>
</tr>
</tbody>
</table>

**MEDIAN TIME TO FIRST SSE (months)**
- **Radium-223** (n=364): 11.8
- **Placebo** (n=183): 8.4

**HR (95% CI):** 0.77 (0.58–1.02)

**P = 0.07**

Cl, confidence interval. HR, hazard ratio. SSE, symptomatic skeletal event.

**Note:** ALSYMPCA was not powered to detect differences between subgroups; P values are for descriptive purpose only and are not adjusted for multiplicity. It is important to note that very few placebo patients were still being followed for SSE at the time of crossover of the Kaplan–Meier curves. Very few placebo patients were still evaluable at later time points on the curve; the hazard ratio is the best interpretation of radium-223 effect over the complete observed time frame.

A significantly higher percentage of patients treated with radium-223, compared with placebo, experienced a meaningful improvement in quality of life according to the FACT-P total score during the period of study drug administration.

FACT-P=Functional Assessment of Cancer Therapy–Prostate.
Mean Change in FACT-P Total Score From Baseline to Week 16

P=0.006

FACT-P=Functional Assessment of Cancer Therapy–Prostate.
ALSYMPCA: Post Hoc Analysis: Time to Initial Opioid Use
(ITT Population; N = 921)

The percentage of patients with treatment-emergent AEs was consistently lower in the radium-223 group compared with the placebo group for all-grade AEs (93% vs 96%), grade 3 or 4 AEs (56% vs 62%), serious AEs (47% vs 60%), and study drug discontinuation due to AEs (16% vs 21%).

---

*Safety population comprised 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.
ALSYMPCA: Adverse Events of Interest
Nonhematologic

Selected Nonhematologic
Treatment-Emergent AEs (All Grades)

- Bone Pain: 50% Radium-223 + BSoC (n=600), 62% Placebo + BSoC (n=301)
- Nausea: 36% Radium-223 + BSoC, 35% Placebo + BSoC
- Fatigue: 26% Radium-223 + BSoC, 26% Placebo + BSoC
- Diarrhea: 25% Radium-223 + BSoC, 15% Placebo + BSoC
- Vomiting: 18% Radium-223 + BSoC, 14% Placebo + BSoC

Most Common Hematologic Treatment-Emergent AEs of Interest (All Grades)

- Anemia: 31 patients (Radium-223 + BSoC) vs. 31 patients (Placebo + BSoC)
- Thrombocytopenia: 6 patients (Radium-223 + BSoC) vs. 12 patients (Placebo + BSoC)
- Neutropenia: 5 patients (Radium-223 + BSoC) vs. 1 patient (Placebo + BSoC)

ALSYMPCA: Safety of cytotoxic chemotherapy following radium-223 chloride (Ra-223) therapy

• In order to better understand the safety of administering chemotherapy following radium-223 therapy, a post hoc analysis was conducted to evaluate the hematologic safety profile in ALSYMPCA patients receiving chemotherapy after completing treatment with the study drug.

• Post hoc analysis of patients (n=147/921/15.9%) receiving chemotherapy after ALSYMPCA:
  - Radium-223 group, 15% (93/614); placebo group, 18% (54/307).

• Most common chemotherapy: docetaxel (n=105), mitoxantrone (n=23), and cyclophosphamide (n=19).

<table>
<thead>
<tr>
<th></th>
<th>Radium-223 (n=93)</th>
<th>Placebo (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to chemotherapy after study drug, days (range)</td>
<td>80.0 (1-667)</td>
<td>64.5 (2-448)</td>
</tr>
<tr>
<td>Median duration of chemotherapy, days (range)</td>
<td>120.0 (1-809)</td>
<td>112.5 (1-863)</td>
</tr>
<tr>
<td>Median OS from start of chemotherapy, months</td>
<td>15.6</td>
<td>14.6</td>
</tr>
</tbody>
</table>

• Hematologic safety profiles for patients receiving chemotherapy after radium-223 were similar to those for patients receiving chemotherapy after placebo.

Question

- Radium 223 may be considered in the management of mCRPC if

1. The patient is experiencing pain due to bone metastasis
2. There are no visceral metastasis
3. Bone marrow function is adequate
4. The patient had already chemotherapy
5. All of the above
SPINAL CORD OR NERVE ROOT COMPRESSION

5-12% of advanced cases

It is an emergency to be treated in 24 ( - 48) hours.

It leads to major functional deficit.

Surgical treatment must be discussed in all cases of vertebral collapse with or without neurological impairment.

Prevention is important: patients with > 20 bone metastasis should undergo MRI imaging of the spine

Bayley et al, Cancer 2001
Talcott et al, Supp Care Cancer 1999
Vertebroplasty
External beam RT to bone

- > 50% of patients will receive RT
- 1x8 Gy vs 5x4 GY vs 10x3 Gy
- Pain relieve in up to 80%
- Occasional complicated b pain flair
- Occasional complicated by fractures
Take home messages

- PCa and ADT have distinct impact on bone in men with PCa.
- Bone consequences of ADT should be evaluated and prevented.
- Bone targeted treatments (BTT) have a positive impact on patients bone complications.
- BTT have potential side effects which should be evaluated and treated.
- Radium 223 has shown benefits in treating pain, preventin SREs and improving OS.
- Patients require an individualized treatment plan including systemic treatment, bone protection, radiation and surgery to prevent and treat SREs.
Prof. Berthold

MALE AGE 69
PROSTATE CANCER
Pathology

Date: May 2006
Subject: Adenocarcinoma of the prostate, Gleason 4+5=9
Content: Stade pT2c N0 M0 with positive margine
Outpatient Clinic

Date: November 01 2009
Metastatic PC

After a fall in PSA, the levels once again began to climb in November 2009 despite LHRH therapy. The patient’s cancer is considered Castration-Resistant Prostate Cancer (CRPC).

He develops pain in his right shoulder and spine.
Imaging

Date: March 15 2010
Subject: Metastatic lesions found
Question: What is the best treatment option for this man?

Answer 1: start docetaxel

Answer 2: start bicalutamide

Answer 3: Give palliative radiation, start denosumab, start systemic treatment for castration-resistant prostate cancer

Answer 4: Give radium-223


The patient also underwent palliative radio therapy
20 Gy (17-24 April 2010) and 8 gy (12 June 2010)
Zoledronic acid 4 mg every months.
Content:

Following palliative radiotherapy the patient’s pain resolved.
The patients PSA level continued to rise and 6 cycles of Docetaxel were administered beginning in June 2010.
Outpatient Clinic

Date: December 15 2010
Subject: Treatment
Content:

Despite Docetaxel therapy PSA levels continued to rise and 5 cycles of Cabazitaxel were given beginning December 2010
After cabazitaxel therapy, the patient’s PSA level began to decrease. Therapy with Abiraterone was initiated in March 2011.
Outpatient Clinic

Date: June 15 2011

Content:

Despite decreasing PSA levels the patient began experiencing pain again in June 2011

The patient underwent radiotherapy (8gy)
Patient Outlook

Case continued

- Palliative RT 20 Gy and 8 Gy
- Docetaxel x6
- Cabazitaxel x5
- Abiraterone
- Bicalutamide

Graph showing changes over time with specific interventions and outcomes.
Question: What is true about pain?

Answer 1: Pain control is a palliative goal.
Answer 2: Pain reduction occur as earlier than PSA responses.
Answer 3: Pain responses are correlated with survival.
Answer 4: All of the above is true.