Radiopharmaceuticals for treating CRPC patients with metastatic bone disease
Bone metastases in prostate cancer

- The most common site of metastasis in prostate cancer
  - In >90% patients with mCRPC
  - ~50% developed skeletal-related events (SREs)
    - fracture, spinal cord compression, radiation or surgery to bone, and hypercalcemia

- Major cause of morbidity and mortality.
Bone-targeted therapy for prostate cancer

- Bisphosphonates
  - Zolendronic acid
- Monoclonal antibody
  - Denosumab
- Radiopharmaceuticals
  - P-32
  - Sr-89
  - Sm-153-HDTMP
  - Ra-223
  - ...

[Diagram showing inhibition of osteoclasts and osteoblasts]
Radiopharmaceuticals for treating malignant bone disease

- **Calcium-mimics**
  - Sr-89
  - Ra-223

- **Phosphonates**
  - P-32 sodium orthophosphate
  - Sm-153-HDTMP (ethylene diamine tetramethylene phosphonate)
  - ...
History of radiopharmaceuticals for treating metastatic bone disease

A brief introduction
Radiopharmaceutical Rx for malignant bone disease

- More than **70 years** of history


- \(\beta\) emitting radionuclide
  - Kills cells in the range of path
  - Physical half-life: 50.5 days

- Dosing vs. management of toxicity
• After 1970’s, several studies focused on the effectiveness of pain relief, comparison with external beam RT …

• A phase III trial in 1993…

RESULTS OF A RANDOMIZED PHASE-III TRIAL TO EVALUATE THE EFFICACY OF STRONTIUM-89 ADJUVANT TO LOCAL FIELD EXTERNAL BEAM IRRADIATION IN THE MANAGEMENT OF ENDOCRINE RESISTANT METASTATIC PROSTATE CANCER

A. T. PORTER, M.D.,¹ A. J. B. McEWAN, M.D.,² J. E. POWE, M.D.,³ R. REID, M.D.,³ D. G. McGOWAN, M.D.,² H. LUKKA, M.D.,⁴ J. R. SATHYANARAYANA, M.D.,⁴ V. N. YAKEMCHUK, M.D.,⁴ G. M. THOMAS, M.D.,⁵ L. E. ERLICH,⁵ J. CROOK, M.D.,⁶ K. Y. GULENCHYN, M.D.,⁶ K. E. HONG, M.D.,⁷ C. WESOLOWSKI, M.D.⁷

and J. Yardley, Ph.D.⁸

Reduced analgesic use

Less new pain sites

Less needs of EBRT
In June, 1993: FDA approved the use of Sr-89 for relief of bone pain in patients with painful skeletal metastases.

Deal with dosing vs. management of toxicity

<table>
<thead>
<tr>
<th>Hematologic events: up to 6 months post-treatment</th>
<th>10 (14.9%)</th>
<th>3 (5.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>9 (13.4%)</td>
<td>7 (12.1%)</td>
</tr>
<tr>
<td>Infection</td>
<td>5 (7.46%)</td>
<td>0</td>
</tr>
<tr>
<td>Receipt of platelets</td>
<td>26 (38.8%)</td>
<td>24 (41.4%)</td>
</tr>
</tbody>
</table>
In the following years

Many new $\beta$ emitting isotopes + phosphonates

Table 1 – Studies comparing pain response between different radionuclides

<table>
<thead>
<tr>
<th>Radionuclides</th>
<th>N</th>
<th>Tumor</th>
<th>Study design</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sr89 vs Sm153</td>
<td>N = 57</td>
<td>Prostate</td>
<td>Non-randomized, retrospective</td>
<td>No difference in pain response rate and toxicity</td>
</tr>
<tr>
<td>Sr89 vs 32P</td>
<td>N = 31</td>
<td>Various tumors</td>
<td>Non-randomized</td>
<td>No difference in pain response rate and response duration. Higher drop in platelet count for P32 but not clinical relevance</td>
</tr>
<tr>
<td>Sr89 vs Re186</td>
<td>N = 44</td>
<td>Various tumors</td>
<td>Non-randomized</td>
<td>No difference in pain response or toxicity. Re188 best improvement in QoL</td>
</tr>
<tr>
<td>Sr89 vs Re186</td>
<td>N = 50</td>
<td>Breast</td>
<td>Randomized</td>
<td>Earlier pain response in Re186, similar duration of response, earlier recovery from hematological toxicity in Re186 (6w versus 12w)</td>
</tr>
<tr>
<td>Sm153 vs Re186</td>
<td>N = 29</td>
<td>Various tumors</td>
<td>Non-randomized</td>
<td>Bone uptake and soft-tissue clearance higher for Sm153</td>
</tr>
<tr>
<td>Sm153-EDTMP vs Re188-HEDP</td>
<td>N = 46</td>
<td>Breast, Prostate</td>
<td>Non-randomized</td>
<td>No differences in pain response, Karnofsky performance score, and bone marrow toxicity</td>
</tr>
<tr>
<td>Re186 vs Sr89</td>
<td>N = 60</td>
<td>Prostate</td>
<td>Non-randomized, retrospective (selection on metastases extent)</td>
<td>No difference in response rate or toxicity</td>
</tr>
</tbody>
</table>
FDA approval

Sm-153 lexicronam
Relief bone pain: confirmed osteoblastic bone mets that enhance on bone scan
Palliation

Deal with dosing vs. management of toxicity

First use of Sr-89
1942

Sr-89
1993

Sm-153 lexicronam
1997

FDA approval
Samarium-153 EDTMP

- Samarium-153 lexicronam
  - Trade name: Quadramet.
- Samarium-153
  - $\beta$ and $\gamma$ emitting radionuclide
  - Physical half-life: 1.9 days
Sm-153 vs. Sr-89

- Sm-153 has:
  - Shorter half-life
  - Lower energy
  - Shorter tissue penetration range
  - Better targeting dose ratio
  - Faster response time

Table 4. Characteristics of some bone seekers used clinically in patients with skeletal metastases

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Physical $t_{1/2}$ (d)</th>
<th>Average particle energy (MeV) per decay</th>
<th>Range in tissue (mm)</th>
<th>Bone surface to red bone marrow dose ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastron ($^{89}$SrCl$_2$)</td>
<td>50.5</td>
<td>0.58</td>
<td>2.4</td>
<td>1.6*</td>
</tr>
<tr>
<td>Quadramet ($^{153}$Sm-EDTMP)</td>
<td>1.9</td>
<td>0.22</td>
<td>0.55</td>
<td>4.4'</td>
</tr>
</tbody>
</table>
Side effects of Sr- 89, Sm-153 EDTMP

- Leukocytes and platelet may decrease by 30%~70% of baseline
  - More frequent and severe in Sr-89 Tx group.
- “Flare” of bone pain may noted, usually within 3 days
Contraindication

- Absolute
  - Acute spinal cord compression
  - Pathological fractures
  - Pregnant woman

- Relative
  - Abnormal hemogram
    - WBC < 3,500 / uL
    - Hemoglobin < 9 g/dl
    - Plt < 60~100 x 10³/ uL
  - Extensive bone marrow involvement
    - “superscan” on bone scan
  - Poor renal function (GFR < 30ml/min)
Pray for being better

- More harm to target
- Less toxicity to normal tissue (bone marrow)

...Think...

- Choices of radioisotopes for therapy
  - Isotopes emitting $\alpha$ or $\beta$ particles
Ionizing radiation

**Energy**

- **ALPHA Particles**
  - Stopped by a sheet of paper

- **BETA Particles**
  - Stopped by layer of clothing or by a few millimeters of a substance such as aluminum

- **GAMMA Rays and X-Rays**
  - Stopped by several feet of concrete or a few inches of lead

**Penetration**
Linear energy transfer (LET)

- Energy transfer per unit length of ionization tract
  - A high LET will attenuate the beam more quickly \(\Rightarrow\) easier shielding
  - Higher concentration of deposited energy \(\Rightarrow\) more severe damage
Biologic effect of radiation
- Indirect and direct effects -

High LET radiation

Low LET radiation

High LET

Low LET
Direct effect

- Break the hydrogen bonding connecting base pairs
- Chemically alter bases
- Break sugar phosphate backbones
  - Single strand breaks (SSB)
  - Double strand breaks (DSB)
Comparison of $\alpha$ and $\beta$ particles

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alpha</th>
<th>Beta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle equivalent</td>
<td>2 protons and 2 neutrons</td>
<td>1 electron</td>
</tr>
<tr>
<td>Relative particle mass</td>
<td>7300</td>
<td>1</td>
</tr>
<tr>
<td>Energy (MeV) per emission</td>
<td>3–8</td>
<td>0.01–2.5</td>
</tr>
<tr>
<td>Range in tissue (μm)</td>
<td>40–100</td>
<td>50–5000</td>
</tr>
<tr>
<td>Lethal hits per cells</td>
<td>1–10</td>
<td>100–1000</td>
</tr>
</tbody>
</table>
β bullet

Collateral damage
可能產生流彈傷害

子彈具穿透力
Target

無辜的旁人

遭流彈擊中
達姆彈 [編輯]

達姆彈又俗稱「炸子」、「開花彈」、「入身殲形子彈」，是一種不具備貫穿力但是具有一定高密度殺傷力「擴張型」子彈。
Alpha emitters
- Shorter range (<0.1 mm)
- High LET
- Low OER
- Survival and palliative benefit

Beta and Gamma emitters
- Longer range (1–10 mm)
- Low LET
- High OER
- Palliative benefit
Alpha therapy in animal study

- Henriksen et al., 2002
- Effect of Ra-223 in skeletal metastases in an experimental animal model (mice)
<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Physical $t_{1/2}$ (d)</th>
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<td>0.55</td>
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<tr>
<td>Alpharadin ($^{223}\text{RaCl}_2$)</td>
<td>11.4</td>
<td>27.4 $^\dagger$</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>
Alpha therapy in human

First Clinical Experience with $\alpha$-Emitting Radium-223 in the Treatment of Skeletal Metastases

Sten Nilsson, Roy H. Larsen, Sophie D. Fosså, Lise Balteskard, Kari W. Borch, Jan-Erik Westlin, Gro Salberg, and Øyvind S. Bruland


- Nilsson et al., 2005
  - Phase I study in 15 patients with breast and prostate cancer
  - Good target to normal bone ratio
  - Effective and mildly toxic
Phase II studies assessing radium-223 in mCRPC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient population</th>
<th>n</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilsson et al., 2014</td>
<td>mCRPC</td>
<td>64</td>
<td>Design: All patients receive a single dose of EBRT. Patients then receive 4 cycles of radium-223 or saline. Primary endpoint(s): Change in bone ALP, Time to first SRE. Key result(s): Decline in bone ALP (−65.6% vs +9.3%, P = 0.0001). Borderline improvement in time to first SRE (HR = 1.75; 95% CI = 0.96–3.14; P = 0.065).</td>
</tr>
</tbody>
</table>

greatly affecting bone-ALP. Secondary endpoints included safety, serum markers of bone turnover (total ALP, procollagen I N propeptide [PINP], C-terminal crosslinking telopeptide of type I collagen [S-CTX-I], type I collagen crosslinked C-telopeptide [ICTP]), serum PSA, and overall survival.
ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III

- Study Design
  - ....

- **Primary Endpoint:** Overall survival

- **Secondary Endpoints:**
  - Time to first SRE, Time to ALP progression, Total ALP response, Time to PSA progression, Safety, QoL
Radium-223 (Alphapharadin)

A Novel Targeted Alpha-Emitter for Bone-Metastatic Castrate-Resistant Prostate Cancer

OLIVER SARTOR, M.D.
North American Principal Investigator, ALSYMPCA trial
Laborde Professor of Cancer Research
Tulane Cancer Center,
Tulane University School of Medicine
New Orleans, LA

More than 900 patients were enrolled in the ALSYMPCA trial, but an early “interim” analysis was performed to ensure that safety and ethical issues were appropriate for trial continuation.

Surprisingly, this interim analysis (performed after 314 deaths) demonstrated a strong and positive survival advantage for those treated with the radium-223. In the interim analysis, patients in the placebo group lived a median of 11.2 months, while the patients in the radium-223 group lived a median of 14.0 months (5). Please note that this trial, along with every other trial has considerable heterogeneity around the median. This compares favorably with other trials performed predominantly in patients previously treated with docetaxel (3,4). The probability of this result being due to chance was less than 2 in 1,000. A final analysis has recently been reported with more follow-up: The median survivals improved with the placebo group living a median of 11.3 months and the radium-223 group treated a median of 14.9 months (8).

The positive survival results led to the trial being stopped at the interim analysis. It was considered unethical to continue the trial with the placebo group.
Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer


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**A  Overall Survival**

- **Hazard ratio, 0.70 (95% CI, 0.58–0.83)**
- **P<0.001**

**Graph:**
- **Radium-223** (median overall survival, 14.9 mo)
- **Placebo** (median overall survival, 11.3 mo)

**Table:**

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radium-223</td>
</tr>
<tr>
<td>0</td>
<td>614</td>
</tr>
<tr>
<td>3</td>
<td>578</td>
</tr>
<tr>
<td>6</td>
<td>504</td>
</tr>
<tr>
<td>9</td>
<td>369</td>
</tr>
<tr>
<td>12</td>
<td>274</td>
</tr>
<tr>
<td>15</td>
<td>178</td>
</tr>
<tr>
<td>18</td>
<td>105</td>
</tr>
<tr>
<td>21</td>
<td>60</td>
</tr>
<tr>
<td>24</td>
<td>41</td>
</tr>
<tr>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>33</td>
<td>1</td>
</tr>
</tbody>
</table>
Radium-223

A novel bone targeted agent for the treatment of mCRPC
Distribution

• Rapidly cleared from the blood
  • At 4 hours, about 4% of the injected radioactivity remained in blood
  • At 24 hours: less than 1% after the injection
• Distributed primarily into bone
• Excreted into intestine
Fig. 2. Microautoradiography from a dog injected with an α-emitting bone seeker. Distribution of α-particle tracks in normal spongy bone (A, left) and an osteoblastic zone (B, right).

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<td>Alpharadin ($^{222}$RaCl$_2$)</td>
<td>11.4</td>
<td>27.4*</td>
<td>&lt;0.1</td>
<td>10.3*</td>
</tr>
</tbody>
</table>
Radium-223 Targets Bone Metastases

- Ra-223 emitting alpha-particles:
  - High LET: 80 keV/um ➔ double-strand DNA breaks
  - Short penetration: < 100um
    ➔ tumour cell killing in adjacent tumour cells
    ➔ minimal damage to surrounding normal tissue
Dream it.
Wish it.
Do it.
Sr-89 / Sm-153 lexidronam
For relief of bone pain in patients with painful skeletal metastases
Palliation

Ra-223
Treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases
Survival benefit

1942
First use of Sr-89

1993~1997
Deal with dosing vs. management of toxicity

2013
ADVANCED DISEASE: ADDITIONAL SYSTEMIC THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER

Studies positive for distant metastases

- Maintain castrate serum levels of testosterone and
denosumab (category 1) or zoledronic acid (category 1) if bone metastases

Symptomatic

- Sipuleucel-T (category 1)
- Secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Abiraterone acetate (category 1)
  - Enzalutamide
  - Ketoconazole
  - Corticosteroids
  - DES or other estrogen
  - Docetaxel
  - Clinical trial

No

- Radium-223 for symptomatic bone metastases (category 1)
- Cabazitaxel (category 1, post-docetaxel therapy)
- Abiraterone acetate or enzalutamide (category 1, post-docetaxel therapy)
- Mitoxantrone
- Salvage chemotherapy
- Docetaxel rechallenge
- Other secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole
  - Corticosteroids
  - DES or other estrogen
  - Sipuleucel-T
  - Clinical trial
  - Best supportive care

Yes

- Radium-223 for symptomatic bone metastases (category 1)
- Salvage chemotherapy
- Docetaxel rechallenge
- Mitoxantrone
- Other secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole
  - Corticosteroids
  - DES or other estrogen
  - Sipuleucel-T
  - Clinical trial
  - Best supportive care

---

b See Principles of Imaging (PROS-B)
k See Principles of Androgen Deprivation Therapy (PROS-F)
r See Principles of Immunotherapy and Chemotherapy (PROS-G)

Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D, page 2 of 2).

Sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG performance status 0-1. Sipuleucel-T is not indicated in patients with hepatic metastases or life expectancy <6 months.

v For patients who are not candidates for docetaxel-based regimens.

Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or hepatic metastases despite lack of symptoms.
Adverse events observed in ALSYMPCA

- Only few substantial difference versus placebo
  - Hematologic: neutropenia, thrombocytopenia
    - anemia (93% vs 88%), lymphocytopenia (72% vs 53%), leukopenia (35% vs 10%), thrombocytopenia (31% vs 22%), and neutropenia (18% vs 5%)
    - < 5% of grade 3, 4

- Gastrointestinal:
  - nausea (36% vs 35%), diarrhea (25% vs 15%), vomiting (19% vs 14%), and peripheral edema (13% vs 10%)
Safety precautions

- **2%** of patients in the Xofigo arm experienced **bone marrow failure** or ongoing pancytopenia

- Prior to first administering Xofigo
  - absolute neutrophil count (ANC) should be > 1500 / uL,
  - platelet count > 100,000 / uL
  - Hemoglobin > 10 g/dL

- Prior to subsequent administrations
  - ANC should be >1000 / uL
  - platelet count > 50,000 / uL

- **Discontinue** Xofigo if hematologic values do not recover within 6 to 8 weeks after the last administration despite receiving supportive care
FUTURE

• Sequence and/or combine with other therapies

• Higher dose-levels

• Long-term toxicity observation

• Broader spectrum of disease

Table 2: FDA mandated studies for radium-223²⁰

<table>
<thead>
<tr>
<th>Study number</th>
<th>Patient population</th>
<th>Final protocol submission</th>
<th>Study completion</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2041-1</td>
<td>mCRPC Bone metastases</td>
<td>9/2013</td>
<td>12/2023</td>
<td>Observational study of 1200 patients. Radium-223 dosed identically to ALSYMPCA study (50 kBq kg⁻¹ every 4 weeks×6). Designed to address risk of long-term bone marrow suppression and risk of developing secondary malignancies.</td>
</tr>
<tr>
<td>2041-2</td>
<td>mCRPC Symptomatic bone metastases, No visceral metastases</td>
<td>12/2013</td>
<td>12/2017</td>
<td>Randomized clinical trial. Designed to address prospectively risk of long-term bone marrow suppression and risk of developing secondary malignancies.</td>
</tr>
<tr>
<td>2041-3</td>
<td>mCRPC Bone metastases</td>
<td>8/2013</td>
<td>9/2016</td>
<td>Prospectively assesses re-treatment with radium-223. Designed to address prospectively risk of long-term bone marrow suppression and risk of developing secondary malignancies.</td>
</tr>
<tr>
<td>2041-4</td>
<td>mCRPC Bone metastases</td>
<td>9/2013</td>
<td>9/2018</td>
<td>Will assess multiple dose levels of radium-223 above 50 kBq/kg. Designed to address prospectively utility of higher dose-levels of radium-223.</td>
</tr>
</tbody>
</table>

FDA: food and drug administration; mCRPC: metastatic castration-resistant prostate cancer.

The End

And the beginning