Isotopes and Palliative Radiotherapy for bone metastases

- Strontium-89
- Samarium-153
- Rhenium-186
- Radium-223
- External beam radiotherapy
Rationale for Bone-seeking Isotope Therapies in Prostate Cancer

• > 90% of patients with advanced prostate cancer have bone metastases which can be the cause of debilitating pain

• Skeletal-related events include spinal cord compression, fracture, and need for surgery or radiation therapy

• Many patients have relatively little extra-osseous disease
Systemic Isotope Therapy

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Type</th>
<th>Energy</th>
<th>Range</th>
<th>Bone: Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strontium-89</td>
<td>beta</td>
<td>1.46</td>
<td>8mm</td>
<td>1.6</td>
</tr>
<tr>
<td>Samarium-153</td>
<td>beta</td>
<td>0.81</td>
<td>3mm</td>
<td>4.4</td>
</tr>
<tr>
<td>Rhenium-186</td>
<td>beta</td>
<td>1.07</td>
<td>4.5mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>gamma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radium-223</td>
<td>alpha</td>
<td>27.8</td>
<td>0.1mm</td>
<td>10.3</td>
</tr>
</tbody>
</table>

Technetium-99, Rhenium-186
Strontium-89 vs External Beam RT in Prostate Ca

Quilty et al 1994 Radioth. Oncol 31;33

• 284 pts with painful bone metastases.

• 3 way randomisation: 200 MBq Strontium-89 65%
  20gy in 5 F local external beam RT 68%
  6Gy x1 hemi-body external beam RT 67%

• At 12 weeks freedom from new painful metastases was 63.9% for SR-89 (p < 0.05) vs 41.7% after local RT
  and 51.1% after hemi-body

• No significant OS difference
Summary
For Strontium and Samarium, there can be good relief of pain for several months, but there is no evidence of a survival benefit. There is mild bone marrow toxicity.
Radium-223: a new treatment for bone metastases

Experiments in mice suggested a marrow-sparing advantage for Radium-226. Henriksen et al 2003

- High linear energy transfer enables DNA double strand breaks even in quiescent cells
- Short particle range limits toxicity to bone marrow
Radium-223: Phase 1

Little myelosuppression after doses between 46 and 250 kBq/Kg

Nilsson 2005
Radium-223: a new treatment for bone metastases

60-70% response rate for bone pain lasting median 8 weeks after single injection

Prolonged effects on ALP
Placebo-Controlled Phase II Study of Radium-223 in Castration-Resistant Prostate Cancer

HR = 0.48; P = 0.017
Median OS 65 vs 46 weeks

<table>
<thead>
<tr>
<th></th>
<th>Radium-223</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>−24%</td>
<td>+45%</td>
<td>0.003</td>
</tr>
<tr>
<td>Total ALP</td>
<td>−46%</td>
<td>+31%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PINP</td>
<td>−63%</td>
<td>+38%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Radium-223</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>155</td>
<td>174</td>
</tr>
<tr>
<td>SAEs</td>
<td>12</td>
<td>19</td>
</tr>
</tbody>
</table>

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

PATIENTS
• Confirmed symptomatic CRPC
• ≥ 2 bone metastases
• No known visceral metastases

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

TREATMENT
6 injections at 4-week intervals
Radium-223 (50 kBq/kg) + Best standard of care
Placebo (saline) + Best standard of care

RANDOMISED
2:1

N = 922

Parker et al. NEJM 2013 369;213-223)
ALSYMPCA Patient Demographics and Baseline Characteristics (ITT; N = 809)

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

ECOG = Eastern Cooperative Oncology Group; WHO = World Health Organization.

Parker et al. 2013
*Treatment ongoing in 107 (21%) patients on radium-223 and 49 (19%) on placebo.
A Overall Survival

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

Radium-223 (median overall survival, 14.9 mo)

Placebo (median overall survival, 11.3 mo)

No. at Risk
Radium-223: 614 578 504 369 274 178 105 60 41 18 7 1 0 0 0
Placebo: 307 288 228 157 103 67 39 24 14 7 4 2 1 0

Parker et al. (2013)
ALSYMPCA Time to First Skeletal-Related Event

![Graph showing time to first skeletal event with hazard ratio, 0.66 (95% CI, 0.52–0.83) and P<0.001. Radium-223 has a median overall survival of 15.6 months, while Placebo has a median overall survival of 9.8 months.]

Parker et al. (2013)
ALSYMPCA Time to First Skeletal-Related Event

B Time to First Symptomatic Skeletal Event

Hazard ratio, 0.66 (95% CI, 0.52–0.83)
P<0.001

Radium-223
(median time to first symptomatic skeletal event, 15.6 mo)

Placebo
(median time to first symptomatic skeletal event, 9.8 mo)

No. at Risk
Radium-223 614 496 342 199 129 63 31 8 8 1 0
Placebo 307 211 117 56 36 20 9 7 4 1 0

Parker et al. (2013)
<table>
<thead>
<tr>
<th></th>
<th>All Grades</th>
<th>Grades 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radium-223 (n = 509)</td>
<td>Placebo (n = 253)</td>
</tr>
<tr>
<td>Haematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>136 (27)</td>
<td>69 (27)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>42 (8)</td>
<td>14 (6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-haematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>217 (43)</td>
<td>147 (58)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>112 (22)</td>
<td>34 (13)</td>
</tr>
<tr>
<td>Nausea</td>
<td>174 (34)</td>
<td>80 (32)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>88 (17)</td>
<td>32 (13)</td>
</tr>
<tr>
<td>Constipation</td>
<td>89 (18)</td>
<td>46 (18)</td>
</tr>
</tbody>
</table>

Parker et al 2013
How do you monitor response to Ra-223?

Baseline
PSA 316
Alk Phos 1921

After Ra-223
PSA 204
Alk Phos 680
External Beam Radiotherapy in Metastatic Prostate Cancer

1. Relief of pain from bone metastasis
2. Relief of spinal cord compression
3. Treatment of the primary cancer
Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases.  


N=288 8vs 30 in 10; patient questionnaire -------→no differences in pain relief or morphine use
Prevention of Spinal Cord Compression

• Spinal Cord Compression (SCC) is the most significant complication due to spinal skeletal metastasis

• 3 – 10% of cancer patients resulting in significant debility and impact on quality of life

• Clinical signs are unreliable indicators of the presence of the level of suspected SCC.

• MRI considered to be a mandatory investigation for detecting SCC and for planning management.

• In prostate cancer – investigations have shown it is possible to detect early radiological signs of impending SCC in asymptomatic patients with or without bone pain.
Launched 2013 Total n=541. CI David Dearnaley (RMH & ICR). ICR Trials Unit.
Sponsor: Cancer Research UK
Conclusions

• Radiotherapy is a useful low toxicity treatment for bone pain in patients with metastases from prostate cancer
• Single fraction external beam treatments are as effective at pain relief as longer schedules
• Systemic bone-seeking isotopes in the past have shown both pain relief and a delay to the next skeletal event
• Radium-223 is a significant advance in isotope treatment, not only causing effective pain relief and delaying further pain, but also prolonging survival