Overall Survival Benefit of Radium-223 Chloride (Alpharadin) in the Treatment of Patients With Symptomatic Bone Metastases in Castration-Resistant Prostate Cancer (CRPC): A Phase III Randomised Trial (ALSYMPCA)

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Disclosures

- C. Parker has served in a consultant or advisory role for Algeta ASA (uncompensated) and Bayer
- D. Heinrich and O. Sartor have served in consultant or advisory roles for Algeta ASA
- B. Bolstad has an ownership interest in and was employed by Algeta ASA until December 2010
- J. Garcia-Vargas is an employee of Bayer HealthCare Pharmaceuticals
- J.M. O’Sullivan, S. Fosså, A. Chodacki, T. Demkow, and A. Cross have nothing to disclose
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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

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
• 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

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

HR: 0.48; 95% CI: 0.26-0.88
\( P = 0.017 \)

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

**PATIENTS**
- Confirmed symptomatic CRPC
- ≥ 2 bone metastases
- No known visceral metastases
- Post-docetaxel or unfit for docetaxel

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

**RANDOMISED**
- 2:1
- N = 922

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

Planned follow-up is 3 years

Clinicaltrials.gov identifier: NCT00699751.
ALSYMPCA Study Endpoints

• Primary Endpoint
  – Overall survival

• Secondary Endpoints
  – Time to first SRE
  – Time to total ALP progression
  – Total ALP response
  – Total ALP normalisation
  – Time to PSA progression
  – Safety
  – Quality of life
ALSYMPCA Statistical Design

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

<table>
<thead>
<tr>
<th></th>
<th>Planned Interim Analysis</th>
<th>Final Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>320</td>
<td>640</td>
</tr>
<tr>
<td>Alpha</td>
<td>0.00306</td>
<td>0.05</td>
</tr>
</tbody>
</table>
ALSYMPCA Planned Interim Analysis

- 314 events from 809 patients randomised at the time of the interim analysis
- Improvement in OS met the predetermined boundary for stopping the trial
- On June 3, 2011, the Independent Data Monitoring Committee (IDMC) recommended stopping the trial early due to evidence of a significant treatment benefit
## 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>
# ALSYMPCA Patient Baseline Characteristics, cont (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></td>
<td>Median (min, max)</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin, g/dL</td>
<td>12.2 (8.5-15.7)</td>
<td>12.1 (8.4-16.4)</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>40 (24-53)</td>
<td>40 (23-50)</td>
</tr>
<tr>
<td>Total ALP, µg/L</td>
<td>213 (32-4661)</td>
<td>224 (29-3225)</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>317 (76-2171)</td>
<td>328 (132-3856)</td>
</tr>
<tr>
<td>PSA, µg/L</td>
<td>159 (3.78-6026)</td>
<td>195 (1.5-14500)</td>
</tr>
</tbody>
</table>
ALSYMPCA Study Drug Treatment Received*

*Based on the number of injections patients had received at the time of the interim analysis. Treatment ongoing in 107 (21%) patients on radium-223 and 49 (19%) on placebo.
ALSYMPCA Overall Survival

HR 0.695; 95% CI, 0.552-0.875
P = 0.00185

Radium-223, n = 541
Median OS: 14.0 months

Placebo, n = 268
Median OS: 11.2 months

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

HR 0.610; 95% CI, 0.461-0.807
P = 0.00046

Radium-223, n = 541
Median: 13.6 months

Placebo, n = 268
Median: 8.4 months
### ALSYMPCA Secondary Endpoints: ALP and PSA

<table>
<thead>
<tr>
<th></th>
<th>Radium-223 n (%)</th>
<th>Placebo n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ALP response (30% reduction)</td>
<td>165 (43)</td>
<td>4 (3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total ALP normalisation*</td>
<td>83 (33)</td>
<td>1 (1)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*In patients who had elevated total ALP at baseline.*

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Total ALP progression</td>
<td>0.163 (0.121 – 0.221)</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Time to PSA progression</td>
<td>0.671 (0.546 – 0.826)</td>
<td>0.00015</td>
</tr>
</tbody>
</table>
## Survival Benefit Across Patient Subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>N</th>
<th>Hazard Ratio</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
<td></td>
<td>0.695</td>
<td>0.552–0.875</td>
</tr>
<tr>
<td>Total ALP</td>
<td>&lt; 220 U/L</td>
<td>452</td>
<td></td>
<td>0.691</td>
<td>0.497–0.962</td>
</tr>
<tr>
<td></td>
<td>≥ 220 U/L</td>
<td>357</td>
<td></td>
<td>0.689</td>
<td>0.504–0.941</td>
</tr>
<tr>
<td>Current Use of Bisphosphonates</td>
<td>Yes</td>
<td>331</td>
<td></td>
<td>0.582</td>
<td>0.397–0.854</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>478</td>
<td></td>
<td>0.752</td>
<td>0.567–0.999</td>
</tr>
<tr>
<td>Prior Use of Docetaxel</td>
<td>Yes</td>
<td>470</td>
<td></td>
<td>0.755</td>
<td>0.565–1.009</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>339</td>
<td></td>
<td>0.611</td>
<td>0.423–0.883</td>
</tr>
<tr>
<td>Baseline ECOG Status</td>
<td>0 or 1</td>
<td>696</td>
<td></td>
<td>0.691</td>
<td>0.535–0.892</td>
</tr>
<tr>
<td></td>
<td>2 or Higher</td>
<td>110</td>
<td></td>
<td>0.731</td>
<td>0.398–1.343</td>
</tr>
</tbody>
</table>
### ALSYMPCA Summary of Patients With Adverse Events: Safety Population* (N = 762)

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

*Patients who received at least 1 injection.
## ALSYMPCA Adverse Events of Interest

<table>
<thead>
<tr>
<th></th>
<th>All Grades</th>
<th></th>
<th>Grades 3 or 4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radium-223 (n = 509)</td>
<td>Placebo (n = 253)</td>
<td>Radium-223 (n = 509)</td>
<td>Placebo (n = 253)</td>
</tr>
<tr>
<td><strong>Haematologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>136 (27)</td>
<td>69 (27)</td>
<td>54 (11)</td>
<td>29 (12)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20 (4)</td>
<td>2 (1)</td>
<td>9 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>42 (8)</td>
<td>14 (6)</td>
<td>22 (4)</td>
<td>4 (2)</td>
</tr>
<tr>
<td><strong>Non-Haematologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>217 (43)</td>
<td>147 (58)</td>
<td>89 (18)</td>
<td>59 (23)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>112 (22)</td>
<td>34 (13)</td>
<td>6 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>174 (34)</td>
<td>80 (32)</td>
<td>8 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>88 (17)</td>
<td>32 (13)</td>
<td>10 (2)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>89 (18)</td>
<td>46 (18)</td>
<td>6 (1)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>
Conclusions

In CRPC patients with bone metastases:

- **Radium-223 significantly prolonged OS**
  - \(P \text{ value} = 0.00185; \text{ HR} = 0.695; 95\% \text{ CI, 0.552-0.875}\)

- **Radium-223 significantly prolonged time to first SRE**
  - \(P \text{ value} = 0.00046; \text{ HR} = 0.610; 95\% \text{ CI, 0.461-0.807}\)

- **Radium-223 was very well tolerated**

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