Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA)

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1The Royal Marsden NHS Foundation Trust, Sutton, UK; 2Karolinska University Hospital, Stockholm, Sweden; 3Akershus University Hospital, Lørenskog, Norway; 4Centre for Cancer Research and Cell Biology, Queen’s University, Belfast, Northern Ireland; 5Radiumhospitalet, Oslo, Norway; 6Hospital Kochova, Chomutov, Czech Republic; 7Centrum Onkologii – Instytut im Sklodowskiej-Curie, Warsaw, Poland; 8Christie Hospital, Manchester, UK; 9Centrallasarettet Växjö, Växjö, Sweden; 10Umeå University, Umeå, Sweden; 11Ullevål University Hospital, Oslo, Norway; 12Mount Vernon Hospital Cancer Centre, Middlesex, UK; 13St. James Hospital, Leeds, UK; 14Weston Park Hospital, Sheffield, UK; 15Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; 16Algeta ASA, Oslo Norway; 17Bayer Healthcare Pharmaceuticals, Montville, NJ, USA; 18Tulane Cancer Center, New Orleans, LA, USA
Disclosures

• C. Parker has served in a consultant or advisory role for Algeta ASA (uncompensated) and Bayer
• S. Nilsson has served in a consultant or advisory role for Algeta ASA
• D. Heinrich, N. Vogelzang, and O. Sartor have served in consultant or advisory roles for Algeta ASA and Bayer; N. Vogelzang has also received grant/research support from Algeta ASA and Bayer
• C.G. O’Bryan-Tear is employed by and has an ownership interest in Algeta ASA
• J. Garcia-Vargas and M. Shan are employees of Bayer HealthCare Pharmaceuticals; M. Shan also holds stock in Bayer
• J.M. O’Sullivan, S. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, and R. Coleman have nothing to disclose
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ALSYMPCA was sponsored by Algeta ASA and Bayer Healthcare Pharmaceuticals.
Background and Rationale

• > 90% of patients with metastatic CRPC have radiologic evidence of bone metastases¹

• Skeletal-related events (SREs) include spinal cord compression, pathological fracture, and need for surgery or external beam radiotherapy²

• Bone metastases are a major cause of death, disability, decreased quality of life, and increased treatment cost³

• 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
Radium-223 Targets Bone Metastases

- 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

**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

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

N = 921

Planned follow-up is 3 years

Clinicaltrials.gov identifier: NCT00699751
ALSYPMA Study Endpoints

• Primary Endpoint
  – Overall survival (OS)

• Secondary Endpoints
  – Time to first SRE
  – Time to total ALP progression
  – Total ALP response
  – Total ALP normalization
  – Time to PSA progression
  – Safety
  – Quality of life
ALSYMPCA OS Analyses

• Planned interim analysis (IA)
  – 314 events from 809 patients randomized at the time of the IA; Cut-off October 2010
  – June 3, 2011 the Independent Data Monitoring Committee (IDMC) recommended stopping the trial early due to evidence of a significant treatment benefit

• Updated analysis
  – 528 events from all 921 patients randomized to the study
  – Updated analysis conducted prior to placebo patients crossing over to Radium-223 and when Radium-223 patients had completed treatment; Cut-off July 2011
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Radium-223 n = 614</th>
<th>Placebo n = 307</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>70.2</td>
<td>70.8</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>575 (94)</td>
<td>290 (95)</td>
</tr>
<tr>
<td>Baseline ECOG score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1</td>
<td>536 (87)</td>
<td>265 (86)</td>
</tr>
<tr>
<td>2</td>
<td>76 (12)</td>
<td>40 (13)</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/superscan</td>
<td>249 (41)</td>
<td>121 (40)</td>
</tr>
<tr>
<td>WHO ladder, cancer pain index ≥ 2, n (%)</td>
<td>345 (56)</td>
<td>168 (55)</td>
</tr>
</tbody>
</table>
## ALSYMPCA Updated Analysis
### Patient Baseline Characteristics (ITT N = 921)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Radium-223 (n = 614)</th>
<th>Placebo (n = 307)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin, g/dL</td>
<td>12.2 (8.5-15.7)</td>
<td>12.1 (8.5-16.4)</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>211 (32-6431)</td>
<td>223 (29-4805)</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>315 (76-2171)</td>
<td>336 (132-3856)</td>
</tr>
<tr>
<td>PSA, µg/L</td>
<td>146 (3.8-6026)</td>
<td>173 (1.5-14500)</td>
</tr>
<tr>
<td>Current bisphosphonates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>250 (40.7)</td>
<td>124 (40.4)</td>
</tr>
<tr>
<td>Prior docetaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>352 (57.3)</td>
<td>174 (56.7)</td>
</tr>
</tbody>
</table>
### ALSYMPCA Updated Analysis

#### Patient Disposition

<table>
<thead>
<tr>
<th></th>
<th>Radium-223 (N = 614)</th>
<th>Placebo (N = 307)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated, n</td>
<td>599</td>
<td>302</td>
</tr>
<tr>
<td>Median number of injections, range</td>
<td>6 (1-6)</td>
<td>5 (1-6)</td>
</tr>
<tr>
<td>Received all 6 injections, n (%)</td>
<td>387 (63)</td>
<td>145 (47)</td>
</tr>
</tbody>
</table>
ALSYMPCA Updated Analysis
Overall Survival

HR = 0.695
95% CI, 0.581, 0.832
P = 0.00007

Radium-223, n = 614
Median OS: 14.9 months

Placebo, n = 307
Median OS: 11.3 months

Month 0 3 6 9 12 15 18 21 24 27 30 33 36 39
Radium-223 614 578 504 369 274 178 105 60 41 18 7 1 0 0
Placebo 307 288 228 157 103 67 39 24 14 7 4 2 1 0
**ALSYMPCA Updated Analysis**

**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>
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<tbody>
<tr>
<td>Overall Survival</td>
<td></td>
<td>921</td>
<td></td>
<td>0.695</td>
<td>0.581–0.832</td>
</tr>
<tr>
<td>Total ALP #</td>
<td>&lt; 220 U/L</td>
<td>517</td>
<td></td>
<td>0.825</td>
<td>0.635–1.072</td>
</tr>
<tr>
<td></td>
<td>&gt;= 220 U/L</td>
<td>404</td>
<td></td>
<td>0.619</td>
<td>0.486–0.788</td>
</tr>
<tr>
<td>Current Use of Bisphosphonates #</td>
<td>Yes</td>
<td>374</td>
<td></td>
<td>0.699</td>
<td>0.525–0.931</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>547</td>
<td></td>
<td>0.736</td>
<td>0.587–0.923</td>
</tr>
<tr>
<td>Prior Use of Docetaxel #</td>
<td>Yes</td>
<td>526</td>
<td></td>
<td>0.710</td>
<td>0.565–0.891</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>395</td>
<td></td>
<td>0.745</td>
<td>0.562–0.987</td>
</tr>
<tr>
<td>Baseline ECOG Status</td>
<td>0 or 1</td>
<td>801</td>
<td></td>
<td>0.675</td>
<td>0.555–0.821</td>
</tr>
<tr>
<td></td>
<td>2 or Higher</td>
<td>118</td>
<td></td>
<td>0.820</td>
<td>0.498–1.351</td>
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</tbody>
</table>
ALSYMPCA Updated Analysis
OS by Stratification Variables: Prior Docetaxel Use

Prior docetaxel use

<table>
<thead>
<tr>
<th>Month</th>
<th>Radium-223 (n=352)</th>
<th>Placebo (n=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>16</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>24</td>
<td>10</td>
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<td>28</td>
<td>5</td>
<td>5</td>
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<tr>
<td>32</td>
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<td>1</td>
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<tr>
<td>36</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Median: Radium-223 = 14.4 months
Median: Placebo = 11.3 months

HR = 0.710
95% CI, 0.565, 0.891
P = 0.00307

NO prior docetaxel use

<table>
<thead>
<tr>
<th>Month</th>
<th>Radium-223 (n=262)</th>
<th>Placebo (n=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>80</td>
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<tr>
<td>8</td>
<td>70</td>
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<td>16</td>
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<td>20</td>
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<tr>
<td>24</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Median: Radium-223 = 16.1 months
Median: Placebo = 11.5 months

HR = 0.745
95% CI, 0.562, 0.987
P = 0.03932
**ALSYMPCA Updated Analysis**

**OS by Stratification Variables: Bisphosphonate Use**

**Current bisphosphonate use**
- **HR = 0.699**
- **95% CI, 0.525, 0.931**
- **P = 0.01378**

**NO current bisphosphonate use**
- **HR = 0.736**
- **95% CI, 0.587, 0.923**
- **P = 0.00775**

---

**Radium-223, n = 250**
- Median: 15.3 months

**Placebo, n = 124**
- Median: 11.5 months

**Radium-223, n = 364**
- Median: 14.5 months

**Placebo, n = 183**
- Median: 11.0 months

---

**Month**
- 0 4 8 12 16 20 24 28 32 36 40

**%**
- 100 90 80 70 60 50 40 30 20 10 0

---

**Current bisphosphonate use**

<table>
<thead>
<tr>
<th>Month</th>
<th>Radium-223</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>0</td>
<td>250</td>
<td>124</td>
</tr>
<tr>
<td>4</td>
<td>232</td>
<td>110</td>
</tr>
<tr>
<td>8</td>
<td>171</td>
<td>76</td>
</tr>
<tr>
<td>12</td>
<td>115</td>
<td>45</td>
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<td>16</td>
<td>61</td>
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<td>6</td>
<td>1</td>
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<tr>
<td>32</td>
<td>2</td>
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</tr>
<tr>
<td>36</td>
<td>0</td>
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---

**NO current bisphosphonate use**

<table>
<thead>
<tr>
<th>Month</th>
<th>Radium-223</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>364</td>
<td>183</td>
</tr>
<tr>
<td>4</td>
<td>331</td>
<td>155</td>
</tr>
<tr>
<td>8</td>
<td>235</td>
<td>102</td>
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<td>12</td>
<td>159</td>
<td>58</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
ALSYMPCA Updated Analysis
OS by Stratification Variables:
Baseline ALP

Total ALP < 220 U/L

- Radium-223, n = 348
  - Median: 17.0 months
- Placebo, n = 169
  - Median: 15.8 months

HR = 0.825
95% CI, 0.635, 1.072
P = 0.14945

Total ALP ≥ 220 U/L

- Radium-223, n = 266
  - Median: 11.4 months
- Placebo, n = 138
  - Median: 8.1 months

HR = 0.619
95% CI, 0.486, 0.788
P = 0.00009

Month %
0 100
10 90
20 80
30 70
40 60
50 50
60 40
70 30
80 20
90 10
100 0

Radium-223 and Placebo counts:
- Radium-223: 348, 325, 246, 179, 107, 52, 31, 9, 2, 0
- Placebo: 169, 151, 115, 75, 44, 20, 11, 5, 1, 0

Month %
0 100
10 90
20 80
30 70
40 60
50 50
60 40
70 30
80 20
90 10
100 0

Radium-223 and Placebo counts:
- Radium-223: 266, 238, 160, 95, 51, 24, 10, 3, 0, 0, 0
- Placebo: 138, 114, 63, 28, 15, 9, 3, 2, 1, 1, 0
**ALSYMPCA Updated Analysis**

**Time To First SRE***

- **HR = 0.64**
- 95% CI, 0.52, 0.78
- \( P < 0.0001 \)

**Radium-223, n = 614**
- Median: 12.2 months

**Placebo, n = 307**
- Median: 6.7 months

<table>
<thead>
<tr>
<th>Month</th>
<th>Radium-223</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>614</td>
<td>307</td>
</tr>
<tr>
<td>3</td>
<td>487</td>
<td>207</td>
</tr>
<tr>
<td>6</td>
<td>332</td>
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<td>9</td>
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<tr>
<td>30</td>
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</table>

*Provisional data*
### ALSYMPCA Updated Analysis
### 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><strong>Total ALP response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30% reduction</td>
<td>233 (47)</td>
<td>7 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>50% reduction</td>
<td>135 (27)</td>
<td>2 (&lt;1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Total ALP normalization</strong> *</td>
<td>109 (34)</td>
<td>2 (1)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to Total ALP progression</strong></td>
<td>0.167 (0.129, 0.217)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td><strong>Time to PSA progression</strong></td>
<td>0.643 (0.539, 0.768)</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

*In patients who had elevated total ALP at baseline.*
**Summary of Patients With Adverse Events: Safety Population**

<table>
<thead>
<tr>
<th>Patients With Adverse Events (AEs), n (%)</th>
<th>Radium-223 n = 600</th>
<th>Placebo n = 301</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grade AEs</td>
<td>558 (93)</td>
<td>290 (96)</td>
</tr>
<tr>
<td>Grade 3 or 4 AEs</td>
<td>339 (57)</td>
<td>188 (63)</td>
</tr>
<tr>
<td>Serious AEs (SAEs)</td>
<td>281 (47)</td>
<td>181 (60)</td>
</tr>
<tr>
<td>Discontinuation due to AEs</td>
<td>99 (17)</td>
<td>62 (21)</td>
</tr>
</tbody>
</table>

*Safety population comprised patients who received at least 1 dose; 1 patient in the placebo group received one injection of Radium-223 (Week 0) and is included in the Radium-223 safety analysis.
# ALSYMPCA Updated Analysis

## AEs of Interest

<table>
<thead>
<tr>
<th>Patients with AEs n, (%)</th>
<th>Radium-223 n = 600</th>
<th>Placebo n = 301</th>
<th>Radium-223 n = 600</th>
<th>Placebo n= 301</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>187 (31)</td>
<td>92 (31)</td>
<td>77 (13)</td>
<td>39 (13)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30 (5)</td>
<td>3 (1)</td>
<td>13 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69 (12)</td>
<td>17 (6)</td>
<td>38 (6)</td>
<td>6 (2)</td>
</tr>
<tr>
<td><strong>Non-Hematologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>300 (50)</td>
<td>187 (62)</td>
<td>125 (21)</td>
<td>77 (26)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151 (25)</td>
<td>45 (15)</td>
<td>9 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>213 (36)</td>
<td>104 (35)</td>
<td>10 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>111 (19)</td>
<td>41 (14)</td>
<td>10 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>108 (18)</td>
<td>64 (21)</td>
<td>6 (1)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>
ALYSMPCA Updated Analysis Conclusions

• Radium-223 compared with placebo in CRPC patients with bone metastases:
  – Significantly prolonged median OS by 3.6 months
    \[(HR = 0.695; \ P = 0.00007)\]
  • 30.5% reduction in risk of death
  – Significantly prolonged median time to first SRE by 5.5 months
    \[(HR = 0.64; \ P < 0.0001)\]

• Further follow-up in all randomized patients continues to show highly favorable safety profile

Radium-223, a first-in-class alpha-emitter, may provide a new standard of care for the treatment of CRPC patients with bone metastases