



Current Perspective

# Effect of radium-223 dichloride (Ra-223) on hospitalisation: An analysis from the phase 3 randomised Alfaradin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial



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## KEYWORDS

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Symptomatic skeletal event;  
Hospitalisation;  
Health care resource use

**Abstract** Symptomatic skeletal events (SSEs) commonly occur in patients with bone metastases, often leading to hospitalisations and decreased quality-of-life. In the ALSYMPCA trial, radium-223 significantly improved overall survival (hazard ratio 0.70, 95% confidence interval [CI] 0.58–0.83,  $P < 0.001$ ) and prolonged time to first SSE (hazard ratio 0.66, 95% CI 0.52–0.83,  $P = 0.00037$ ) and subsequent SSE (hazard ratio 0.65, 95% CI 0.51–0.83,  $P = 0.00039$ ) versus placebo in patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases. Health care resource use (HCRU), including hospitalisation events and days, were prospectively collected in ALSYMPCA. We assessed health care resource use for the first 12 months post-randomisation. Significantly fewer radium-223 (218/589; 37.0%) versus placebo patients (133/292; 45.5%) had at least one hospitalisation event ( $P = 0.016$ ). However, mean number of hospitalisation events per patient was similar (radium-223 0.69 versus placebo 0.79,  $P = 0.226$ ), likely due to the significantly longer follow-up time for radium-223 (7.82 months versus 6.92 months for placebo;

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$P < 0.001$ ). There were significantly fewer hospitalisation days per patient for radium-223 (4.44 versus 6.68, respectively,  $P = 0.004$ ). The reduction in hospitalisation days with radium-223 was observed both before first SSE (2.35 days versus 3.36 days, respectively) and after SSE (7.74 days versus 9.19 days, respectively). Our data suggest that this reduced hospital days along with the survival benefit and reduction in time to SSEs with radium-223 treatment may contribute to improvements in health-related quality-of-life in patients with castration-resistant prostate cancer with symptomatic bone metastases (ALSYMPCA ClinicalTrials.gov number, NCT00699751.).

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## 1. Introduction

Skeletal-related events (SREs) commonly occur in patients with bone metastases and prostate cancer [1–5] and are associated with increased morbidity (including significant pain) and mortality [1,3,5,6] and decreased quality-of-life (QoL) [3,6]. In addition, SREs are associated with increased health care resource use (HCRU) [1,3,6] and costs [1,7,8]. Patients with prostate cancer and bone metastases and  $\geq 1$  SRE have a 2-fold increase in emergency department visits and a 4-fold increase in hospitalisations versus those without SREs [1], and costs are substantially higher, especially when SRE treatment requires concurrent surgery [8]. Considering the increased burden of metastatic castration-resistant prostate cancer (mCRPC), there is a need for effective therapies targeted at bone metastases for the prevention and management of SREs and improving patient outcomes.

The ALSYMPCA trial results demonstrated that radium-223 versus placebo improves overall survival and prolongs time to first and subsequent symptomatic skeletal events (SSEs) in patients with bone metastases from CRPC [9,10]. In this *post-hoc* analysis from ALSYMPCA, we evaluated the effect of radium-223 on HCRU, including hospitalisation days before first SSE and after SSE, over the first 12 months following treatment randomisation.

## 2. Methods

The ALSYMPCA study design (phase 3, randomised, double-blind, placebo-controlled) and patient enrolment criteria have been published [9]. Briefly, patients with CRPC with symptomatic bone metastases and no known visceral metastases were randomly allocated in a 2:1 ratio to receive radium-223 plus best standard of care or placebo plus best standard of care. Radium-223/matching placebo treatments were administered at 4-week intervals for a total of 6 injections. The study protocol was approved by the institutional review boards at each participating study center, and all patients provided written informed consent.

In the current analysis, we evaluated the effect of radium-223 on HCRU over the first 12 months following

treatment randomisation. The first 12 months following treatment initiation with radium-223 is considered the most clinically meaningful and reflective of treatment effect on HCRU during which most patients would be evaluable and most HCRU would be used [11]. Hospitalisation event rate within a treatment group was calculated as the number of patients with at least one hospitalisation event divided by the total number of patients; a Fisher's exact test was used for treatment group comparison. The following HCRU outcomes were prospectively collected at each study visit from randomisation through week 52 and totalled by category for each patient: hospitalisation events (in-patient admissions), hospitalisation days, physician visits, nursing home stays, home health care hours, and adult day care visits. Means and standard deviations were reported for each HCRU category, and non-annualised resource use between treatments was compared via t-tests. The analysis population included only patients from the intention-to-treat population (i.e. all randomised patients) who had HCRU data available. All analyses were conducted using SAS 9.4 software (SAS Institute Inc).

The further analysis of hospitalisation days compared treatment differences before first SSE and after SSE. An SSE was defined as use of external-beam radiation therapy to relieve bone pain, new symptomatic pathologic vertebral or non-vertebral bone fractures, spinal cord compression, or tumour-related orthopaedic surgical intervention. All events had to be clinically apparent. The pre-SSE population included all patients with observations before first SSE, and post-SSE included all patients with observations after SSE. Patients with a known history of SSE before study entry or before first study treatment were not included in the pre-SSE population but were included in the post-SSE population.

## 3. Results

A total of 921 patients were randomised in ALSYMPCA, 614 to radium-223 and 307 to placebo and 20 (15 radium-223, 5 placebo) patients withdrew without receiving study drug. Of the remaining 901 patients, 599 radium-223 patients and 302

placebo patients received treatment. Baseline demographic and clinical characteristics, including bisphosphonate use, were well balanced between the radium-223 and placebo groups [9]. A total of 41% of the patients in the radium-223 group and 40% of the patients in the placebo group reported bisphosphonate use at baseline [9]. For each HCRU category, data were available for 578–589 radium-223 patients and 287–292 placebo patients (details in Fig. 1).

Significantly fewer radium-223 patients (218/589; 37.0%) than placebo patients (133/292; 45.5%) had at least one hospitalisation event (two-sided  $P$ -value = 0.016). The primary reasons for hospitalisation are listed in Table 1. Among patients with data on hospitalisation, the mean follow-up time was 7.82 months for radium-223 and 6.92 months for placebo ( $P < 0.001$ ). The mean number of hospitalisation events per patient was similar for radium-223 and placebo (0.69 versus 0.79, respectively; 95% confidence interval for difference in means [−0.27, 0.06];  $P = 0.226$ ; Table 2). In contrast, treatment with radium-223 significantly reduced mean hospitalisation days per patient versus placebo (4.44 versus 6.68, respectively; 95% confidence interval for difference in means [−3.77, 0.72];  $P = 0.004$ ; Fig. 2A).

As shown in Table 2, there were no statistical differences between treatments for the other HCRU categories analysed.

### 3.1. Hospitalisation days according to SSE occurrence

Of the 874 (586 radium-223, 288 placebo) patients with data on hospitalisation days (Fig. 1), 27 (16 radium-223

Table 1

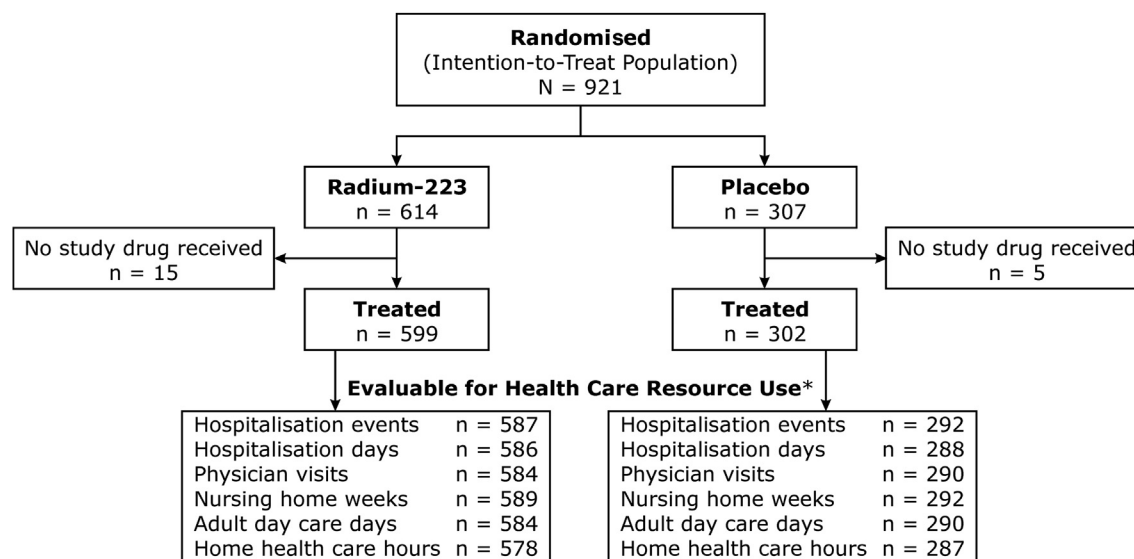
Primary reasons for hospitalisation.<sup>a</sup>

Reason for hospitalisation	Radium-223 N = 589	Placebo N = 292
At least 1 hospitalisation, n (%)	218 (37.0%)	133 (45.5%)
P-value for difference between treatments	$P = 0.016$	
	<b>Radium-223</b>	<b>Placebo</b>
Total number (no.) of hospitalisations	423	237
No. of hospitalisations with a listed reason <sup>b</sup>	420	230
Bone pain, no. of hospitalisations (%)	42 (10.0%)	31 (13.5%)
Pain, no. of hospitalisations (%)	39 (9.3%)	12 (5.2%)
Anaemia, no. of hospitalisations (%)	36 (8.6%)	22 (9.6%)
Infection, no. of hospitalisations (%)	32 (7.6%)	13 (5.7%)
Blood transfusion, no. of hospitalisations (%)	14 (3.3%)	5 (2.2%)
Spinal cord compression, no. of hospitalisations (%)	9 (2.1%)	10 (4.3%)

<sup>a</sup> Five most common reasons in each group; the 6th reason in each group is listed for purposes of table balance (i.e. spinal cord compression in the radium-223 group and blood transfusion in the placebo group).

<sup>b</sup> For 3 hospitalisations in the radium-223 group and for 7 in the placebo group, the reason for hospitalisation was not listed.

and 11 placebo) patients had known SSE before study entry/before first study treatment and therefore were excluded from the pre-SSE analysis population. These 27 patients, however, were among the 271 patients in the post-SSE population. The mean follow-up times were 6.7 months for radium-223 and 5.4 months for placebo before first SSE, and 4.6 and 4.5 months, respectively, after SSE. Hospitalisation days per patient increased in both treatment arms following SSE from 2.35 to 7.74 days for radium-223 and from 3.36 to 9.19 days for



\*Includes only those patients from the intention-to-treat population with health care resource use data available.

Fig. 1. Patients evaluable for the health care resource use analysis.

Table 2

Health care resource use for first 12 months following treatment randomisation (ITT population).

Health care resource use	Radium-223 N = 614	Placebo N = 307	Treatment difference (SD)	P-value
Hospitalisation events (SD)	0.69 (1.20)	0.79 (1.15)	−0.10 (1.19)	0.226
Hospitalisation days (SD)	4.44 (10.05)	6.68 (12.12)	−2.24 (10.78)	0.004
Physician visits (SD)	4.25 (6.97)	4.24 (6.63)	0.01 (6.86)	0.980
Nursing home weeks (SD)	0.12 (0.98)	0.22 (1.84)	−0.10 (1.33)	0.292
Adult day care days (SD)	0.42 (3.17)	0.38 (3.49)	0.04 (3.28)	0.876
Home health care hours (SD)	7.59 (57.64)	4.12 (19.52)	3.48 (48.45)	0.321

Data are means (standard deviation, SD); p-values are from a t-test comparing treatment differences and may represent biased comparisons due to differences in observation times.

Data on hospitalisation events, hospitalisation days, physician visits, nursing home weeks, adult day care days, and home health care hours were available for 587, 586, 584, 589, 584, 578 patients, respectively, in the radium-223 arm and for 292, 288, 290, 292, 290, 287 patients, respectively, in the placebo arm.

ITT = intention-to-treat.

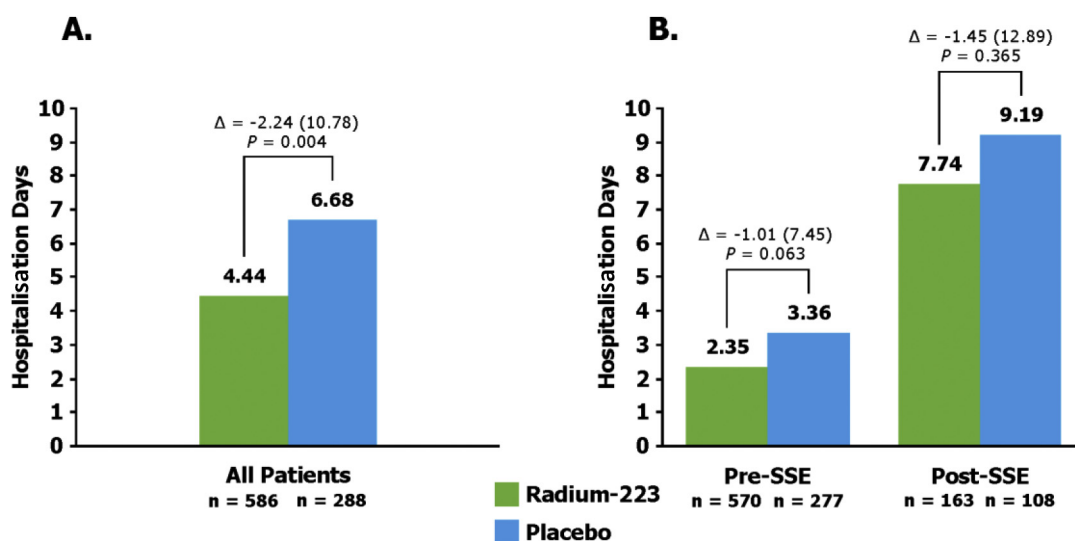


Fig. 2. Mean hospitalisation days per patient for the first 12 months following treatment randomisation. Treatment differences (SD) are also shown. (A) All patients evaluable for hospitalisation days. (B) Patients evaluable for hospitalisation days before first SSE and after SSE (by definition, the pre-SSE population included all patients with observations before first SSE, and post-SSE included all patients with observations after SSE). SD, standard deviation; SSE, symptomatic skeletal event.

placebo. Compared with placebo, treatment with radium-223 was associated with fewer hospitalisation days per patient before first SSE and after SSE (Fig. 2B).

#### 4. Discussion

The present analysis evaluated HCRU over the first 12 months following treatment randomisation to either radium-223 or placebo. Significantly fewer patients treated with radium-223 versus placebo had at least one hospitalisation event (37.0% versus 45.5%,  $P = 0.016$ ). Overall, radium-223 patients experienced a 12.7% reduction in hospitalisation events per patient ( $P = 0.226$ ) and a 33% reduction in hospitalisation days per patient ( $P = 0.004$ ). These results may possibly be explained by the delayed time to first SSE and the overall reduced number of SSEs with radium-223 treatment [10].

Skeletal-related events result in increased HCRU, and hospitalisation due to SREs occurs in up to 82% of patients with prostate cancer and bone metastases, with frequency dependent on the type of SRE [3,4,7,8]. A reduction in skeletal morbidity has important cost consequences. Average HCRU costs are about \$30,000 higher in patients with SREs versus without SREs, with 64% being inpatient costs [8]. Considering the benefits of radium-223 on SSEs and the influence of skeletal complications on HCRU, we further explored the impact of radium-223 on hospitalisation days before first SSE and after SSE to determine whether the reduction in hospitalisation duration remains the same.

Spinal cord compression, an SSE commonly requiring hospitalisation, has been associated with the longest duration of stay [3]. In ALSYMPCA, the risk for spinal cord compression was significantly reduced with radium-223 ( $P = 0.03$ ) [10]. Considering SSEs

overall, radium-223 patients experienced fewer events than placebo patients (33% versus 38%, respectively) and median time to first SSE (15.6 months versus 9.8 months) and subsequent SSE (~16.5 months versus 10.1 months) were significantly ( $P < 0.0004$ ) longer for radium-223 [10]. The present analysis confirms the influence of SSEs and radium-223 on HCRU. Radium-223 versus placebo was associated with fewer hospitalisation days pre-SSE and post-SSE versus placebo (Fig. 2B). The decrease in hospitalisation days pre-SSE indicates an effect beyond delaying SSE, which could be related to the reduced need for pain management. Time to external beam radiation therapy and time to initial opioid use were significantly longer with radium-223 ( $P = 0.001$  and  $P = 0.002$ , respectively) [12]. The decrease in hospitalisation days post-SSE may possibly be explained by a delay or avoidance of subsequent SSE [10].

Length of hospital stay has been reported to increase as prostate cancer progresses to include bone metastases and SREs [6]. Likewise, we found that hospitalisation days (duration) increased after SSE in both treatment arms (Fig. 2B). Moreover, previous analyses have shown that radium-223 provides more meaningful improvements in QoL versus placebo, and that the QoL treatment benefits are greater before the occurrence of SSE [9,13,14]. These findings suggest the importance of radium-223 treatment before an SSE arises.

In our analysis, differences in hospital-related HCRU favoured radium-223 and were statistically significant versus placebo for mean number of hospitalisation days per patient and percentage of patients with at least one hospitalisation event. However, while treatment with radium-223 resulted in fewer mean number of hospitalisation events per patient, the difference compared to placebo was not statistically significant. This is likely due to the significantly longer follow-up time for radium-223 patients (7.82 months versus 6.92 months for placebo patients,  $P < 0.001$ ), which was not accounted for in our analyses and could have minimised the observed treatment differences, leading to potential bias against radium-223. Both the radium-223 and placebo groups had similar rates of bisphosphonate use at baseline, and we did not examine HCRU based on this parameter. However, considering that overall survival was not influenced by bisphosphonate use in the primary analysis data set [9], we would not expect bisphosphonate use to have an influence on HCRU outcomes.

## 5. Conclusion

Radium-223 improves overall survival and reduces the risk for SSEs in men with CRPC and bone metastases. The benefits of radium-223 are further extended by a reduction in hospitalisation days, as observed before first SSE and after SSE. Together these data suggest that

use of radium-223 may contribute to reduced HCRU, including reduced hospitalisation days possibly through delayed time to first and subsequent SSE, and improvements in health-related QoL.

## Author contributions

CP, OS, SN, PC and LZ were involved in conception or design. CP, OS, NJV, SN, PC and JR-S were involved in drafting the manuscript. PC, LZ and JR-S were involved in the statistical analysis. LZ was involved in obtaining funding. NJV, JMO, PC and LZ were involved in administrative, technical or material support. OS, PC and LZ were involved in the study supervision. All authors were involved in the acquisition, analysis, or interpretation of data, critical revision of the manuscript for important intellectual content, review of the manuscript and approval of the final manuscript.

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## Conflict of interest statement

CP has received grants or funding from Bayer and has received honoraria from Bayer and Janssen. OS has received grants or funding from, served as a consultant for and received honoraria from Bayer. REC has received grants or funding to his institution from Bayer, Amgen and Celgene. NJV has served as a consultant for Bayer, Genentech, Exelexis, Medivation and Pfizer and has served on speaker bureaus for BMS, Pfizer, Genentech, Novartis, Sanofi Aventis, Dendreon and Bayer. SN has served as a consultant for Bayer. JMO has received grants or funding from Bayer and has served as a consultant for and on the speakers bureaus for Astellas, Bayer, Sanofi and Janssen. PC was employed by the Pharmaceuticals Division of Bayer at the time of the study. LZ is employed by the Pharmaceuticals Division of Bayer. JR-S has served as a statistical consultant for Bayer Pharma AG.

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## References

- [1] McDougall JA, Bansal A, Goulart BH, McCune JS, Karnopp A, Fedorenko C, et al. The clinical and economic impacts of skeletal-related events among medicare enrollees with prostate cancer metastatic to bone. *Oncologist* 2016;21:320–6.
- [2] Aly A, Onukwugha E, Woods C, Mullins CD, Kwok Y, Qian Y, et al. Measurement of skeletal related events in SEER-Medicare: a comparison of claims-based methods. *BMC Med Res Methodol* 2015;15:65.
- [3] Bahl A, Hoefeler H, Duran I, Hechmati G, Garzon-Rodriguez C, Ashcroft J, et al. Health resource utilization associated with skeletal-related events in patients with advanced prostate cancer: a European subgroup analysis from an observational, multinational study. *J Clin Med* 2014;3:883–96.
- [4] Hagiwara M, Delea TE, Saville MW, Chung K. Healthcare utilization and costs associated with skeletal-related events in prostate cancer patients with bone metastases. *Prostate Cancer Prostatic Dis* 2013;16:23–7.
- [5] Nørgaard M, Jensen AØ, Jacobsen JB, Cetin K, Fryzek JP, Sørensen HT. Skeletal related events, bone metastasis and survival of prostate cancer: a population based cohort study in Denmark (1999 to 2007). *J Urol* 2010;184:162–7.
- [6] Pockett RD, Castellano D, McEwan P, Oglesby A, Barber BL, Chung K. The hospital burden of disease associated with bone metastases and skeletal-related events in patients with breast cancer, lung cancer, or prostate cancer in Spain. *Eur J Cancer Care (Engl)* 2010;19:755–60.
- [7] Roghmann F, Antczak C, McKay RR, Choueiri T, Hu JC, Kibel AS, et al. The burden of skeletal-related events in patients with prostate cancer and bone metastasis. *Urol Oncol* 2014;33:17.e9–18.
- [8] Jayasekera J, Onukwugha E, Bikov K, Mullins CD, Seal B, Hussain A. The economic burden of skeletal-related events among elderly men with metastatic prostate cancer. *Pharmacoeconomics* 2014;32:173–91.
- [9] Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013;369:213–23.
- [10] Sartor O, Coleman R, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. *Lancet Oncol* 2014;15:738–46.
- [11] Cislo P, Reuning-Scherer J. Effects of radium-223 dichloride (Ra-223) on risk for hospitalization and health care resource use in the phase 3 ALSYMPCA trial. *J Clin Oncol* 2014;32(Suppl. 30). abstract 21.
- [12] Parker C, Finkelstein SE, Michalski JM, O'Sullivan JM, Bruland Ø, Vogelzang NJ, et al. Efficacy and safety of radium-223 dichloride in symptomatic castration-resistant prostate cancer patients with or without baseline opioid use from the phase 3 ALSYMPCA trial. *Eur Urol* 2016 Jun 22. pii: S0302–2838(16)30272-X. doi: 10.1016/j.eururo.2016.06.002. [Epub ahead of print].
- [13] Cislo P, Sartor O, Reuning-Scherer J, Shan M, Zhan L, Parker C. Effects of radium-223 dichloride (Ra-223) on health-related quality of life (HRQoL) assessed by the EQ5D utility scores in ALSYMPCA. *Eur Urol* 2015;14(2):e673.
- [14] Nilsson S, Cislo P, Sartor O, Vogelzang NJ, Coleman RE, O'Sullivan JM, et al. Patient-reported quality-of-life analysis of radium-223 dichloride from the phase III ALSYMPCA study. *Ann Oncol* 2016;27:868–74.