Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG Collaborator and original sponsor: Algeta ASA	
Study Number:	15305 (BC1-03)	NCT00667199 EudraCT2004-000299-15
Study Phase:	II	
Official Study Title:	A double-blind, dose-response phase II, multicentre study of radium-223 (Alpharadin®) for the palliation of painful bone metastases in hormone refractory prostate cancer patients	
Therapeutic Area:	Oncology	
Test Product		
Name of Test Product:	Radium-223 dichloride (Xofigo [Alpharadin], BAY88-8223)	
Name of Active Ingredient:	Radium-223 dichloride	
Dose and Mode of Administration:	Radium-223 was administered as a single, slow intravenous injection in one dose (of the four doses from 5, 25, 50, and 100 kBq/kg body weight (b.w.)). A second injection at a dose of 50 kBq/kg b.w. could be administered after the 16-week study period was completed, at the discretion of the investigator.	
Reference Therapy/Placebo		
Reference Therapy:	None	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	A single dose of radium-223 was given. A second injection could be administered after the completion of the 16-week study period, at the discretion of the investigator.	
Studied period:	**Date of first subjects' first visit:**	30 MAY 2005
	Date of last subjects' last visit:	06 OCT 2009
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	The original final version of the protocol (dated 01 July 2004) was subject to five protocol amendments, including some key changes to the design and conduct of the study. All subjects were recruited after the approval of Protocol Amendment 2. Amendment 1 (dated 22 SEP 2004) introduced: changes to the inclusion and exclusion criteria and blood sample parameters. Amendment 2 (dated 25 FEB 2005) altered the study to a double-blind, dose-ranging study to assess four dose levels (the previous study design assessed a dose of 100 kBq/kg b.w.). To this end, changes were made to key sections such as the study title and objectives. In addition, a change was made to include only subjects	

	with prostate cancer to keep the subject population as homogenous as possible (the previous study design included subjects with breast or prostate cancer). To this end, changes were made to the sections relating to the subject population, such as the inclusion criteria. Further, the primary endpoint was also clarified and the secondary endpoints were extended. The sample size was also increased from 35 to 100 subjects to allow for the change in study design. Amendment 3 (dated 15 SEP 2005) edited the inclusion criteria and the list of study centres and principal investigators, and clarified the analysis of b-ALP at a single laboratory. Amendment 4 (dated 10 JUL 2006) was introduced to allow the administration of a second injection of radium-223 after the initial 16-week Post-treatment Period had been completed. Assessments to be performed after the second injection were also defined. Amendment 5 (dated 10 OCT 2007) was introduced to exclude subjects with imminent or established spinal cord compression based on clinical findings and/or MRI.
Study Centre(s):	The study was conducted at 16 centers in Sweden, Germany, France and the United Kingdom.
Methodology:	All subjects suffering from bone pain (with at least a score 2 on the Brief Pain Inventory [BPI]) due to multiple bone metastases secondary to prostate cancer were enrolled in the study. Bone scintigraphy was performed within 6 weeks before study drug administration to ascertain osteoblastic metastatic disease and osteoblastic activity at painful sites. Following a prestudy screening visit and a 1-week baseline period during which subjects completed a diary of pain assessments (measured on a visual analog scale [VAS]) and baseline analgesic consumption, each subject received radium-223 based on the randomized dose level and individual body weight. The subjects were randomized in an equal ratio (25 planned subjects for each dose) Further assessments of pain (using the VAS and the BPI form), analgesic consumption, and safety were performed in the 16-week Post-treatment Period. During this period, the subjects continued to complete the diary and attend the study visits at Weeks 2, 4, 8, 12, and 16. Follow-up visits took place 6, 9, 12, 18, and 24 months after the first injection of the study drug for assessment of disease progression, survival, and possible long-term toxicity. A second injection of radium-223 at a dose of 50 kBq/kg b.w. could be administered to the subjects after completion of the 16-week study period, at the discretion of the investigator. If applicable, assessments of safety were performed 2 and 4 weeks after the second injection of the study drug. Physical examination and clinical laboratory test data were collected at

	the baseline, week 2, 4, 8, 12, 16 and 6-, 9-, 12-, 18- and 24-month visits. Concomitant cancer medications ongoing or starting after 16 weeks and concomitant cancer therapies were recorded. Adverse events (AEs) were recorded if they were judged to be related to the study treatment.
Indication/ Main Inclusion Criteria:	Indication: Hormone-refractory prostate cancer with bone metastases Inclusion criteria: Confirmed adenocarcinoma of the prostate; hormone refractory with evidence of progressive disease; multifocal skeletal metastases confirmed by scintigraphy within previous 6 weeks; bone pain with a score of at least 2 on BPI (average pain) despite adequate use of analgesics that correlated with areas of increased uptake on scintigraphy.
Study Objectives:	**Primary:** The primary objective of the study was to investigate whether there is a dose-response relationship for radium-223 in subjects with painful bone metastases secondary to prostate carcinoma regarding the palliation of bone pain. **Secondary:** The secondary objective was to find the most efficacious dose with an acceptable safety profile. The objective of the 24-month follow-up report was to document long-term toxicity and overall survival at 2 years post-treatment.
Evaluation Criteria:	**Efficacy (Primary):** • Pain index, based on a combination of the change in diary pain rating (recorded by subjects on a VAS) and the change in analgesic consumption, from baseline to Weeks 2, 4, 8, 12 and 16. There were six possible pain index outcomes, from 1=complete response to 6=pain progression **Efficacy (Secondary):** • The change in BPI pain severity index mean and sum (mean and sum of items 1-4), BPI functional interference index mean and sum (mean and sum of items 6-12), and BPI item 5 (pain relief from medication), from baseline to Weeks 2, 4, 8, 12 and 16; the change in (i) pain at rest and (ii) pain while moving (recorded on a VAS) from baseline to Weeks 2, 4, 8, 12 and 16; duration of pain relief; survival. **Safety:** The following safety variables were evalutated in the study: • Adverse events from the day of study drug administration up to 24 months were reported if related to the study drug. • Physical examination performed from baseline up to 24 months and consisting of general physical examination, respiratory examination, cardiovascular examination, and abdominal examination. During the physical examination visit, Karnofsky performance status and disease progression were assessed by the

	investigator. Any physical examination finding that was classified by the investigator as a clinically significant change (worsening compared to previous examination) that resulted in a change in subject management was considered an AE, if considered related to the study treatment. • Possible long-term toxicities (acute myeloid leukemia [AML], myelodysplastic syndrom [MDS], aplastic anemia, primary bone cancer, or other diagnoses) were reported up to 24 months after first injection of study medication • Deaths • Clinical laboratory measurements, with emphasis on hematological toxicity: clinically significant worsening from the previous examination resulting in a change in subject management was to be regarded as an AE.
Statistical Methods:	**Population:** ITT analysis set: The ITT analysis set consisted of all subjects who received at least one injection of study medication. PP analysis set: The PP analysis set consisted of all subjects who received at least one injection of study medication and had a score of at least 2 on BPI average pain, confirmed by an average diary pain rating in diary of at least ring the Baseline Period. Summary statistics were provided for the safety data. **Efficacy (Primary):** Efficacy data were presented using summary statistics for descriptive analysis. In addition, the analysis of continuous and ordinal data was conducted using the Jonckheere-Terpstra test for trends in dose response. All statistical analyses of efficacy were performed using data from subjects included in the PP analysis set. Efficacy analysis for the primary endpoints was also performed using the ITT analysis set. **Efficacy (Secondary):** Survival data were analyzed using Kaplan-Meier estimates and log-rank-test for difference between treatments. **Safety:** Summary statistics were provided for the safety data.
Number of Subjects:	The following table summarizes the disposition of the study subjects:

	Number (%) of subjects				
	5 kBq/kg b.w.	25 kBq/kg b.w.	50 kBq/kg b.w.	100 kBq/kg b.w.	Total
Randomized	26 (100.0)	25 (100.0)	25 (100.0)	24 (100.0)	100 (100.0)
Received 1st injection	26 (100.0)	25 (100.0)	25 (100.0)	24 (100.0)	100 (100.0)
Received 2nd injection		1 (4.0)	3 (12.0)	2 (8.3)	6 (6.0)
Completed Week 16 or later	17 (65.4)	18 (72.0)	20 (80.0)	18 (75.0)	73 (73.0)
12-month visit	10 (38.5)	6 (24.0)	8 (32.0)	8 (33.3)	32 (32.0)
18-month visit	6 (23.1)	1 (4.0)	5 (20.0)	5 (20.8)	17 (17.0)
24-month visit	4 (15.4)	1 (4.0)	2 (8.0)	1 (4.2)	8 (8.0)

Study Results

Results Summary — Subject Disposition and Baseline

All subjects who entered the study were Caucasian. The mean (standard deviation [SD]) age of all the subjects was 68.9 (7.5) years; 27 subjects (27%) were aged ≥75 years. There was a slight baseline imbalance in Eastern Co-operative Oncology Group (ECOG) performance score (range 0 to 2), with a higher percentage of subjects in the 50 and 100 kBq/kg groups having a score of 2 (ambulatory and capable of self care, but unable to carry out work activities). There was a wide range in the time interval between the diagnosis of prostate cancer and the time of study drug injection (range 0.1 to 20 years) and between the diagnosis of bone metastases and the time of study drug injection (range 0.04 to 16.5 years). A larger percentage of subjects in the higher dose groups had an extent of disease (EOD) grade of 3 (>20 sites) or 4 (superscan) compared with the two lowest dose groups. Mean baseline PSA values were higher in the 5 kBq/kg group (by approximately 280−350 µg/L) compared with the other groups, but there was large variation in individual values in all the treatment groups.

Prior and Concomitant Therapies and Medications:

Previous (and completed) medication for prostate cancer was recorded for 87 subjects (87%) overall, with a slightly lower percentage recorded in the 100 kBq/kg b.w. dose group (75% subjects versus 88−96% subjects in other dose groups). A larger percentage of subjects in the 100 kBq/kg b.w. dose group received baseline analgesic medications with a World Health Organization level of at least 3, i.e., strong opioids (65% versus 40% subjects in the other dose groups). A total of 39 subjects (39%) had at least one concomitant therapy, with a slightly smaller proportion receiving at least one therapy in the 100 kBq/kg b.w. dose group (29% subjects) compared with the other dose groups (approximately 40%). The majority of these therapies were blood transfusion (21% subjects) and external radiotherapy (24%). A smaller percentage of subjects in the highest dose group had external radiotherapy compared with the other dose groups (8% versus 30%). A large proportion of subjects in all dose groups (≥75%) received a concomitant opioid and other analgesics or antipyretics.

A total of 78 subjects (78%) completed the study to 16 weeks. Of the 22 subjects (22%) who withdrew within the 16-week Post-treatment Period, the highest percentages occurred in the lowest dose groups: 7 subjects (27%) and 7 subjects (28%) in the 5 and 25 kBq/kg b.w. dose groups, respectively. In the two highest dose groups (50 and 100 kBq/kg b.w.), 5 subjects (20%) and 3 subjects (13%) discontinued within this period. The most common overall reason for withdrawal during this period was death (12 subjects [12%]); again, a higher percentage of subjects died in the lowest dose groups: 4 (15%) and 5 (20%) subjects in the 5 and 25 kBq/kg b.w. dose groups, respectively, whilst only 3 subjects died in the two highest dose groups during the 16 weeks Post-treatment Period. Other reasons for withdrawal were "other" (6 subjects [6%]), consent withdrawn (3 subjects [3%]) and AE (1 subject [1%]).

In total, 34 completed follow-up at Month 12. There was no trend with dose in proportion discontinuing, with 11, 42%; 6, 24%; 8, 32% and 9, 38% in the 5, 25, 50 and 100 kBq/kg b.w. dose groups respectively, completing the 12-month assessments. Again, the most common overall reason for withdrawal was death, which occurred in 6 (23%), 6 (24%), 7 (28%) and 10 (42%) of subjects in the 5, 25, 50 and 100 kBq/kg b.w. dose groups, respectively. The second major reason for withdrawal was "other," affecting 6 (24%), 4 (16%), and 2 (8%) of subjects in the 25, 50 and 100 kBq/kg b.w. dose groups respectively. In the 5 kBq/kg b.w. dose group, one subject withdrew due to an AE and one withdrew consent (reason given was bad general condition); one more subject withdrew consent in the 50 kBq/kg b.w. dose group (reason given was long distance to travel and pain).

A total of 26 subjects (26%) withdrew during the period 12 to 24 months; 7 subjects (26.9%) in the 5 kBq/kg b.w. group, 5 (20.0%) in the 25 kBq/kg b.w. group, 6 (24%) in the 50 kBq/kg b.w. group, and 8 (33.3%) in the 100 kBq/kg b.w. group. The most common reason overall for withdrawal in this period was death; 7 subjects (26.9%) in the 5 kBq/kg b.w. group, 4 (16.0%) in the 25 kBq/kg b.w. group, 3 (12%) in the 50 kBq/kg b.w. group, and 6 (25%) in the 100 kBq/kg b.w. group.

Results Summary — Efficacy

Primary efficacy

Pain index score: The Jonckheere-Terpstra test for trends was statistically significant at Week 2 (p=0.035), indicating a significant dose-response at this time point; the highest mean pain index scores were in the 5 and 25 kBq/kg b.w. dose groups (4.8 and 4.1, respectively) compared with lower mean scores in the 50 and 100 kBq/kg b.w. dose groups (both 3.9). At Week 4, the mean (and/or median) pain index score decreased in each dose group, indicating an improvement in pain response at this time point, with the best response recorded in the 100 kBq/kg b.w. dose group. At Week 8, the best response was again recorded in the 100 kBq/kg b.w. dose group and reflected a further improvement in pain response compared with Week 4.

The median value (2.0) indicated a marked pain response in this dose group, compared with baseline, and this was generally maintained throughout the 16-week Post-treatment Period. At Week 8, a decrease in pain index score was also seen in the 25 kBq/kg b.w. dose group, although not to the same extent as for the 100 kBq/kg b.w. dose group, and this was also maintained at Weeks 12 and 16. The results of the PP analysis set were supported by pain index data for the ITT analysis set.

Pain Responders; Pain response (pain index categories: minimal (4), moderate (3), marked (2) and complete (1) pain response) was seen in 54%, 59%, 68% and 68% of the subjects at Week 4 in the 5, 25, 50 and 100 kBq/kg b.w. respectively. At Week 8 the response rates were 40%, 63%, 56% and 71%.

Secondary efficacy

Mean diary pain VAS scores: These were decreased in Week 2 in all dose groups, being slightly lower in the two highest dose groups (30 and 35 mm) compared with the two lowest dose groups (38 and 38 mm). The mean scores continued to decrease at Weeks 4 and 8 in all dose groups. At Weeks 12 and 16, there were some further mean decreases and generally mean VAS scores remained lower than baseline scores in all dose groups (range of mean scores: 19-22 mm at Week 16). The largest mean (and percentage mean) decreases were recorded for the 25 kBq/kg b.w. dose group, and the smallest mean decreases were mainly recorded for the 5 kBq/kg b.w. dose group.

Analgesic consumption: In the two highest dose groups, the concomitant medication for bone pain was stable in a larger proportion of subjects compared to the two lowest dose groups at Weeks 2 and 4, and larger in the 100 kBq/kg b.w. dose group at Week 8. In the two lowest dose groups, a higher percentage of subjects had increased bone pain medication compared with the two highest dose groups, at Weeks 2, 4 and 8.

Change in BPI pain severity index mean: All dose groups had a similar mean (SD) BPI pain severity index mean score at baseline (pre-dose on Day 1): 3.9 (1.3), 4.2 (1.8), 4.1 (1.5) and 4.4 (1.3) in the 5, 25, 50 and 100 kBq/kg b.w. dose groups, respectively. The mean (and median) score decreased progressively in all dose groups at Weeks 2, 4 and 8, such that the mean (SD) scores at Week 8 were: 2.9 (1.7), 2.8 (2.3), 2.7 (1.2) and 2.4 (1.4) in the 5, 25, 50 and 100 kBq/kg b.w. dose groups, respectively. At Weeks 12 and 16, average scores remained decreased compared with baseline in all dose groups, indicating improvements in pain severity index even in the lowest dose group. The Jonckheere-Terpstra test for trends was statistically significant at Week 8 (p=0.040), indicating a significant dose response at this time point. The mean percentage change from baseline at Week 8 was -19.5%, -28.4%, -29.1% and -40.1% for the 5, 25, 50 and 100 kBq/kg b.w. dose groups,

respectively, showing a greater mean decrease (improvement) in the highest dose group. Greater percentage decreases from baseline were also observed in the two highest dose groups at Weeks 12 and 16, compared with the two lowest dose groups.

Change in BPI pain severity index sum: A similar picture to that for the BPI pain severity index mean was apparent. The mean score decreased progressively in all dose groups at Weeks 2, 4 and 8, and mean scores again remained decreased compared with baseline at Weeks 12 and 16, in all dose groups. The Jonckheere-Terpstra test for trends was statistically significant at Week 8 (p=0.040), indicating significant dose- response at this time point.

Change in BPI functional interference index mean and sum: A similar pattern to that for the BPI pain severity index mean and sum was again apparent. There were mean decreases from baseline in all dose groups, with progressive decreases at Weeks 2, 4 and 8, persisting at Weeks 12 and 16. However, the Jonckheere-Terpstra test for trends in dose response did not reach statistical significance at any time point (p>0.05).

Duration of pain relief: This was longer in the two highest dose groups (both with a mean of 44 days) compared with the 5 and 25 kBq/kg b.w. dose groups (28 and 35 days, respectively). Some subjects (across all dose groups) had pain relief lasting over 100 days. The Jonckheere-Terpstra test for trends in dose response was not statistically significant (p>0.05).

Survival: In total, 42 subjects died in the study up to 12 month after first injection of study drug, 10 (38.5%), 12 (48%), 8 (32%) and 12 (50%) in the 5, 25, 50 and 100 kBq/kg b.w dose groups, respectively. There was no apparent difference in duration of survival between dose groups (p-value 0.78, Log rank test). In the majority of subjects that died (36 of 42), death was caused by progression of metastatic prostate cancer, reported in 9 (90%), 11 (92%), 6 (75%) and 10 (83%) unique subjects in the 5, 25, 50 and 100 kBq/kg b.w dose groups, respectively (percentages expressed as proportion of deaths in each dose group). None of the other deaths (6 of 42) was attributed to study drug.

In total, 32 (32.0%) subjects attended the 12-month follow-up visit (a further two subjects withdrew more than 12 months after first injection of study drug, but did not attend a 12-month or later study visit). Eight subjects (8.0%) completed the 24-month follow-up visit, while 20 subjects died. By 24 months after first injection of study medication, 8 (8.0%) subjects were alive in the whole study population, 4 (15.4%) in the 5 kBq/kg b.w. group, 1 (4.0%) in the 25 kBq/kg b.w. group, 2 (8.0%) in the 50 kBq/kg b.w. group, and 1 subject (4.2%) in the 100 kBq/kg b.w. group.

There were 20 deaths overall (20.0%) in the period 12 to 24 months following injection, 7 (26.9%), 4 (16.0%), 3 (12.0%) and 6 (25.0%) subjects in the 5, 25, 50 and 100 kBq/kg b.w. groups, respectively. In 19 of the 20 subjects who died, death was caused by progression of metastatic prostate cancer. In 16 of these subjects, the organ affected by metastases was reported as skeletal; 1 subject reported brain metastases; 1 had both skeletal and brain affected; and 1 had skeletal, lymph and brain affected. In all cases where the physician's opinion was recorded, the deaths were judged to be unlikely to be related to study drug. The last subject died of chronic heart insufficiency and chronic obstructive lung disease.

Six subjects withdrew from the study between months 12 and 24 for reasons other than death during the study (1 withdrew consent; for the remaining 5, the reason was recorded as "other"). Two of these subjects withdrew more than 12 months after first injection of study drug, but did not attend a 12-month or later study visit.

There was no significant difference between the dose groups in overall survival time, defined as the number of weeks from first injection of study drug to death (Log rank test; p=0.57). There were no diagnoses of acute myelogenous leukaemia (AML), myelodysplastic syndrome (MDS), aplastic anaemia, primary bone cancer or other new diagnosis recorded on the termination report of subjects who terminated the study between the 12-month and 24-month visits.

Results Summary — Safety

A total of 97 subjects (97%) reported a total of 564 AEs. The proportions of subjects in the four treatment groups with any AE were comparable. The most frequently reported individual AEs (reported by ≥10% subjects overall) were: nausea (43%); fatigue (26%); vomiting (24%); diarrhoea (22%); constipation (20%); decreased haemoglobin (15%); urinary tract infection (14%); peripheral oedema (12%); and anaemia (11%). There was no apparent increasing incidence with increasing dose level for any of these AEs.

Of the less frequently reported AEs of potential interest, tumour flare and bone pain were reported by a greater percentage of subjects in the two lowest dose groups. Conversely, AEs of lymphopenia, decreased platelet count, decreased white blood cell count and anorexia were mainly reported in the two highest dose groups.

Of the 73 of subjects (73%) that continued in the study at the end of the Post-treatment Period (Week 16), 32 completed follow-up at Month 12. There was no relationship between dose and the proportion discontinuing.

The most common overall reason for withdrawal was death. The second major reason for withdrawal was "other," the most frequent reason given being lost to follow up. AEs were required to be reported during the Follow-up Period if considered related to study drug. Although a number of unrelated AEs were also reported, just one related AE was reported, mild diarrhoea shortly following a second injection of radium-223. There was no evidence of long-term toxicity.

In the period 12 to 24 months after the first injection of the study medication, there were no reports of AEs that were considered to be related to study medication.

In 19 of the 20 subjects who died, death was caused by progression of metastatic prostate cancer, and all deaths where the physician's opinion was recorded were judged to be unlikely to be related to study medication.

No related AEs or serious adverse events (SAEs) were reported in the 12-month to 24-month follow-up period. Thus, no AEs were the reason for study termination.

There were no diagnoses of AML, MDS, aplastic anaemia, primary bone cancer, or any other new diagnosis reported in any of the treatment groups in the period 12 to 24 months following injection of radium-223.

Conclusion(s)

In this study, the following conclusions were made:

- Radium-223 reduced bone pain in subjects with painful bone metastases secondary to prostate carcinoma.
- At 2 weeks post injection the primary endpoint (pain index) showed a significant dose-response relationship following a single injection of radium-223 (5, 25, 50 and 100 kBq/kg b.w.), with trends towards a dose response at 4 and 8 weeks. The best pain response in terms of the pain index was observed in the highest dose group (100 kBq/kg b.w.) up to 8 weeks after radium-223 injection.
- All doses of radium-223 showed a benign safety profile. In this study, there was no trend of increasing overall incidence of AEs, SAEs or deaths with increasing dose of radium-223.
- There was no evidence of long-term toxicity up to 24 months following injection of radium-223.
- There was no evidence of any difference in survival time between the four doses of radium-223.
- No deaths and no AEs were judged to be related to the study treatment.

• A single injection of radium-223 at dose levels of 5, 25, 50, and 100 kBq/kg seemed to be generally safe and well tolerated in this study population.			
Publication(s):	Nilsson S, Strang P, Aksnes AK, Franzen L, Olivier P, Pecking A, et al. A randomized, dose–response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. Eur J Cancer. 2012;48(5):678-86.		
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