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:	15304 (BC1-04)	NCT00337155 EudraCT: 2005-003680-22
Study Phase:	II	
Official Study Title:	A double blind, randomised, dose finding, repeat dose, phase II, multicentre study of Alpharadin® for the treatment of patients with hormone-refractory prostate cancer and skeletal metastases	
Therapeutic Area:	Oncology	
Test Product		
Name of Test Product:	Radium-223 dichloride (Xofigo [Alpharadin], BAY 88-8223)	
Name of Active Ingredient:	Radium-223 dichloride	
Dose and Mode of Administration:	Eligible subjects were randomised with equal probability to receive 25, 50, or 80 kBq/kg of body weight of the study drug. The required volume of the study drug was calculated using the subject's body weight, the dose level, and a volume correction factor to correct for physical decay of radium-223. The study drug was administered intravenously at 6 weekly intervals.	
Reference Therapy/Placebo		
Reference Therapy:	Not applicable	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	Three injections of the assigned dose of Alpharadin (25, 50, or 80 kBq/kg body weight) were administered at intervals of 6 weeks (total dose 75, 150, or 240 kBq/kg).	
Studied period:	**Date of first subjects' first visit:**	05 MAY 2006
	Date of last subjects' last visit:	02 DEC 2009
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	The study was conducted according to the final approved study protocol and its two amendments: Amendment No. 1 (dated 28 JUN 2007) specified the following changes: • There was an addition of measurement of Serum C-terminal cross-linking telopeptide of type I collagen (s-CTX-I), a biochemical marker of bone resorption; this was expected to add valuable information about the efficacy of Alpharadin and did not affect the volume of blood drawn for the efficacy analysis. • The time period of 6 weeks between bone scintigraphy and subject inclusion was extended to 12 weeks; and the time period of 6 weeks between abdominal/pelvic computed tomography (CT) or	

	magnetic resonance imaging (MRI) and subject inclusion was extended to 8 weeks for practical reasons. • Clarifications to the protocol were also introduced in the amendment related to primary and secondary objectives of the trial; pre-treatment and treatment period; allowed previous cytotoxic chemotherapy; general rules of dose delay or discontinuation of treatment; guidelines for specific adverse events (AEs); and sample size dependence of the amount of protocol deviations. Amendment No. 2 (dated 31 OCT 2007) specified the following changes: • Addition of a new exclusion criterion: Subjects with imminent or established spinal cord compression, based on clinical findings and/or MRI, were excluded. • Change in reporting and assessment of AEs: the time period for reporting AEs was extended from 3 months to 6 months from the first Alpharadin injection so that the recording period for subjects that only received 1 or 2 doses of Alpharadin was the same as that for subjects who received all three doses.
Study Centre(s):	This study was conducted at 21 centres in the UK, Czech Republic, France, Poland, and Spain.
Methodology:	This was a Phase II, multi-center, efficacy and safety study with a randomized, double-blind, repeated-dose, parallel-group, dose-finding design in which all doses were potentially active. Subjects had progressive castration-resistant prostate cancer and skeletal metastases, but could be asymptomatic. Subjects participated in a Pre-treatment Period, a Treatment Period, a Post-treatment Period, and a Follow-up Period: • The Pre-treatment Period was 2 weeks before the first injection of Alpharadin during which the eligibility of the subjects was evaluated. After providing written informed consent, subjects underwent screening and baseline assessments including demography, medical history, prostate cancer history (including Gleason grade, previous treatment and extent of disease), physical examination, performance status (Eastern Cooperative Oncology Group [ECOG] grade), pain diary, concomitant medication and clinical safety laboratory tests. At least three measurements of prostate specific antigen (PSA) were obtained at intervals of 1 week. • The Treatment Period was the 12-week period after the first injection of Alpharadin. Treatment consisted of three injections of Alpharadin given at intervals of 6 weeks. Eligible subjects were randomized with equal probability to receive 25, 50, or 80 kBq/kg body weight, the same dose being given on each dosing occasion (total doses of 75, 150, or 240 kBq/kg). The subject visited the hospital every 3rd week during the treatment period for measurements of efficacy and safety parameters. • The Post-treatment Period was the 12-week period after the last injection of Alpharadin. The subject visited the hospital 3, 6, and 12 weeks after the last injection of Alpharadin (Week 16, Week 19, and Week 24). • The Follow-up Period was the period after Week 24 until 24 months

	after the first injection of Alpharadin. Subjects visited the hospital 9, 12, 18, and 24 months after the first injection of Alpharadin for evaluation of safety, long-term toxicity, and survival. Efficacy was assessed during the Treatment and Post-treatment Periods (up to Week 24) using measurements of PSA, bone- and total alkaline phosphatase (ALP), and s-CTX-I in a central laboratory, recording of skeletal-related events (SREs), and assessments of pain using a pain diary, recording use of analgesia, and the Brief Pain Inventory (BPI) form. During the Follow-up Period, these assessments (with the exception of the pain diary) continued; however, it was not anticipated that Alpharadin would influence these assessments, which were reported as safety measures in this period. Survival was assessed throughout the study. Safety was assessed using AEs, concomitant medication, physical examination and clinical laboratory tests. All AEs with onset before Week 24 were reported. Those AEs (including serious adverse events (SAEs)) with onset more than 24 weeks after the first injection of Alpharadin were reported only if they came to the investigator's attention and were judged related to Alpharadin.
Indication/ Main Inclusion Criteria:	Indication: • Prostate cancer • Neoplasm metastasis Inclusion criteria: Histologically or cytologically confirmed adenocarcinoma of the prostate; symptomatic or asymptomatic and hormone-refractory, with documented rising PSA and multifocal skeletal metastases confirmed by bone scintigraphy.
Study Objectives:	**Primary:** To compare the proportion of patients with hormone-refractory prostate cancer and skeletal metastases showing a prostate specific antigen (PSA) response (PSA decrease $\geq$ 50% from baseline, confirmed three weeks later) on three different repeat dose regimens of Alpharadin. **Secondary:** • To compare the maximum percent decrease of PSA from baseline in subjects on three different repeat dose regimens of Alpharadin • To compare the effect on bone-specific alkaline phosphatase (bone-ALP) of three dose regimens of Alpharadin • To examine for correlation between bone-ALP and PSA • To compare the effect of three dose regimens of Alpharadin on s-CTX-I • To examine for correlation between s-CTX-I and PSA • To determine the effect of three different repeat dose regimens of Alpharadin on time to skeletal-related events • To determine the effect of these three repeat dose regimens of Alpharadin on pain response in subjects with pain • To determine the safety, tolerability, and long-term toxicity of

	these three repeat dose regimens • To determine the time to death
Evaluation Criteria:	**Definitions:** • **PSA response**: A decrease in PSA from baseline of at least 50%. • **Time to confirmed PSA progression**. For subjects with a PSA response: The interval from the first day of treatment until the day the value increased by at least 50% from the nadir to >5 ng/mL. For non-responders: The interval from the first day of treatment until the day the value had increased at least 25% above the nadir to >5 ng/mL. • **Confirmed PSA response and confirmed PSA progression**: Values were to be confirmed by a second value obtained at least 3 weeks after the first. For this purpose, a value at least 19 days later was considered acceptable. **Efficacy (Primary):** • Primary endpoint: Confirmed PSA response • Primary analysis variable: Proportion of subjects in each dose group with a confirmed PSA response **Efficacy (Secondary):** • PSA: Maximum relative decrease in PSA; change in PSA; time to confirmed PSA progression • Bone-ALP: Confirmed response; change in bone-ALP; time to confirmed bone-ALP progression • s-CTX-I: Confirmed response; change in s-CTX-I; time to confirmed s-CTX-I progression • Time to first SRE; total number of SREs per subject • Change in analgesic consumption, categorized as reduced, increased, or stable using the the World Health Organisation (WHO) pain ladder • Pain index, based on change in BPI item 3 (average pain last week) and change in analgesic consumption; time to pain progression; BPI pain severity index; BPI functional interference index; BPI item 5 (pain relief); change in diary pain rating. • Survival: Time to death, recorded up to 2 years from the first injection/Month 24 Visit; where agreed to by the subject, this information was recorded after discontinuation from the study. With the exception of survival, efficacy was analyzed up to the Week 24 Visit. **Safety:** All AEs were recorded up to Week 24 regardless of relation to Alpharadin. During the Follow-up Period from Week 24 until Month 24, only (serious) adverse events that the investigator considered related to Alpharadin were recorded. Physical examination, performance status, extent of disease, clinical laboratory tests, long-term toxicity, and disease progression were evaluated.
Statistical Methods:	**Efficacy:**

Statistical analysis of proportions, including the primary efficacy end point (proportion of subjects with confirmed PSA response) and secondary efficacy end points (proportions with confirmed PSA progression, bone-ALP response or progression, and s-CTX-I response or progression, and survival), was conducted using a Jonckheere-Terpstra test for trends. Pair-wise comparisons between doses were conducted using Fisher's exact test when the initial Jonckheere-Terpstra test was statistically significant ($p < 0.05$). Proportions were presented at specified time points with point estimates and 95% confidence intervals.

Continuous or ordinal data (secondary efficacy variables [change in PSA, bone-ALP, s-CTX-I, pain index, and BPI variables]) were evaluated using Jonckheere-Terpstra test for trends.

Time to event data (secondary efficacy variables [progression of PSA, bone-ALP, s-CTX-I, pain, death]) were evaluated using log-rank test for trends. Time to event data were additionally presented using Kaplan-Meier estimates for the median and 1st and 3rd quartiles and the number of censored observations. Subjects were censored at the last date for which information was available up to the second anniversary of the first injection (or the Month 24 visit if later). For other efficacy variables, subjects with no events were censored at the later of the last available time point or the Week 24 visit.

Correlations between PSA and bone-ALP, PSA and s-CTX-I, and bone-ALP and s-CTX-I were determined at each visit for pooled data, as well as for each dose group. Due to the expected skewed nature of the data, the Spearman rank correlation was presented.

Safety:

Descriptive statistics were used.

Number of Subjects:

The table below gives the number of subjects in the three treatment groups.

Number of subjects in the different analysis sets

Analysis Set	Dose group*			All
	25 kBq/kg	50 kBq/kg	80 kBq/kg	
Planned	39	39	39	117
Safety	41	39	42	122
Intention-to-treat	41	40	41	122
Per-protocol	37	36	39	112
Completed Week 24	32	31	33	96
Completed Month 12	27	25	22	74
Completed Month 24	11	14	11	36

* One patient was randomised to the 50 kBq/kg dose group but in error was treated with 80 kBq/kg. He is included in the Safety and Per-protocol Sets as treated and in the Intention-to-treat Set as randomised.

Study Results

Results Summary — Subject Disposition and Baseline

In total, 122 subjects were enrolled with 39 (32%) to 42 (34%) subjects receiving at least one dose in each dose group.

Overall, 96 subjects (79%) of the 122 subjects completed the Treatment and Post-treatment Period up to Week 24 with a comparable proportion (78%, 80%, and 79% in the 25 kBq/kg, 50 kBq/kg and 80 kBq/kg groups, respectively) in each dose group.

In total, 74 of 122 subjects (61%) completed follow-up to Month 12 (66%, 64%, and 52% in each dose group) and 36 of 122 subjects (30%) completed follow-up to Month 24 (27%, 36%, and 26% in each dose group).

More than one reason could be given for study termination. The most frequently reported reason was death. In total, 62 subjects discontinued the study due to death: 72% of the 86 subjects who terminated the study and 51% of the total study population. Overall, 59% of the 25 kBq/kg dose group, 49% of the 50 kBq/kg dose group, and 45% of the 80 kBq/kg dose group terminated the study due to death. Conversely, a somewhat higher proportion of the subjects in the 50 kBq/kg and 80 kBq/kg dose groups discontinued due to disease progression (21% and 19%, respectively) than in the 25 kBq/kg dose group (10%). Relatively small numbers of subjects discontinued due to other reasons (adverse events, 5%; investigator's request, 2%; subject's request, 2%; other, 11%) with no imbalance between doses.

Subjects in the 50 kBq/kg dose group were slightly younger (mean age: 66.8 ± 9.4 years) and heavier (mean 86.1 ±17.5 kg) than those in the 25 kBq/kg and 80 kBq/kg dose groups (71.6 ± 6.7 years, 81.0 ±11.9 kg and 69.4 ±8.5 years, 82.3 ±12.9 kg, respectively). However, body mass index was comparable across the three dose groups (27.4 ± 4.1 kg/m^2 in the 25 kBq/kg group, 28.3 ±5.5 kg/m^2 in the 50 kBq/kg group, and 27.9 ±3.3 kg/m^2 in the 80 kBq/kg group). Three subjects were not Caucasian (one in the 80 kBq/kg dose group was Oriental-Asian; two in the 50 kBq/kg dose group were "other").

Results Summary — Efficacy

Primary efficacy variable:

This study met the primary endpoint by demonstrating a statistically significant dose-response relationship for confirmed 50% PSA response. The primary efficacy variable was the proportion of subjects with a confirmed PSA response. In the Per-protocol Set, this occurred in 0 (0 %), 2 (5.6 %), and 5 (12.8 %) of the subjects in the 25 kBq/kg, 50 kBq/kg, and 80 kBq/kg dose groups, respectively ($p = 0.0297$ (Jonckheere-Terpstra test for dose response; pairwise comparison between 25 kBq/kg and 80 kBq/kg dose groups was borderline significant, $p = 0.0548$).

Results in the Intention-to treat Set were similar ($p = 0.0290$). This shows that there was a positive relation between the dose of Alpharadin and the proportion of subjects with confirmed PSA response as defined, with the highest dose being statistically more effective than the lowest dose.

Secondary efficacy variables and other analyses:

PSA

- There was a statistically significant dose-response relation in time to confirmed PSA response ($p = 0.0205$); the median time to confirmed PSA response could not be estimated due to the low numbers of responders.
- The maximum relative decrease in PSA was comparable in the 50 kBq/kg and 80 kBq/kg dose groups (mean 40.4% and 35.5%, respectively), both greater than in the 25 kBq/kg dose group (mean 16.8%); the test for a dose-response was not statistically significant. The median time after the first injection to the maximum decrease was 10 or 11.5 weeks in each treatment group with no statistically significant dose response.

- The median PSA increased in all dose groups at all time points. However, increases in the 50 kBq/kg and 80 kBq/kg dose groups were comparable and smaller than in the 25 kBq/kg dose groups. The test for dose response was statistically significant at Week 16 ($p = 0.050$) and close to significant at Week 10 ($p = 0.075$), Week 13 ($p = 0.052$) and Week 24 ($p = 0.052$).
- The median time to confirmed PSA progression was 6 weeks in the 25 kBq/kg dose group and 12 weeks in the 50 kBq/kg and 80 kBq/kg dose groups (not statistically significant overall or separately for responders or non-responders).

Bone-ALP

- The proportions of subjects with a confirmed bone-ALP response were 16.2% (6 subjects), 66.7% (24 subjects), and 65.8% (25 subjects) in the 25 kBq/kg, 50 kBq/kg and 80 kBq/kg dose groups, respectively (test for trend, $p < 0.0001$; pairwise comparisons between 25 kBq/kg and both 50- and 80 kBq/kg dose groups also statistically significant). The median time to confirmed bone-ALP response could not be estimated in the 25 kBq/kg dose group and was 9 to 10 weeks in the 50 kBq/kg and 80 kBq/kg ($p < 0.0001$ for dose-response).
- The median bone-ALP decreased in all dose groups at all time points, especially in the 50 kBq/kg and 80 kBq/kg dose groups ($p < 0.05$ for dose response at all time points). After Week 16, the median percent decrease in bone-ALP declined compared with the preceding time point as median values began to increase back towards baseline.
- There was no statistically significant difference in the proportion of subjects with confirmed bone-ALP progression or the time to confirmed progression.

s-CTX-I

There was no dose-related trend in the proportion of subjects with a confirmed s-CTX-I response, confirmed progression, or the time to confirmed response. There were statistically significant dose-response relations in time to confirmed progression (12 weeks for the 25 kBq/kg dose group; not estimable for the 50 kBq/kg dose group; 18.3 weeks for the 80 kBq/kg dose group) and in the changes from baseline at Weeks 16 to 24.

Correlations between PSA, bone-ALP and s-CTX-I

There was a high degree of correlation between each of these three biomarkers in all dose groups and at most time points.

Skeletal-related events

In total, 62 of the 112 subjects in the Per-protocol Set had at least one skeletal-related events with a total of 71 events being reported (each type of event being counted only once per subject). The most frequent skeletal-related events reported were increase in pain, increase in analgesic consumption, and external radiotherapy. The proportion of subjects reporting at least one event (41%, 50%, and 44% in the 25 kBq/kg, 50 kBq/kg, and 80 kBq/kg dose groups, respectively) and the number of events reported (20, 25, and 26, respectively) were comparable between dose groups.

Pain

All subjects:

- The pain index was based on a combination of the score of BPI item 3 and the analgesic consumption for each subject. A high proportion of subjects were missing pain index data, which was available for 86 of the 112 subjects in the Per-protocol Set. The initial pain response appeared slower in the 25 kBq/kg dose group than in the 50 kBq/kg and 80 kBq/kg groups. At Week 16 and Week 19, around half (50 to 60% of subjects in each group) had a pain response. By Week 24, the percentage with a pain response had

decreased to 44 to 52%. In total, 68%, 54%, and 58% in the 25 kBq/kg, 50 kBq/kg, and 80 kBq/kg dose groups, respectively, experienced pain progression. The proportion with pain progression and the time to pain response and pain progression showed no statistically significant dose-response relation.

- The median change from baseline in pain severity index in the 25 kBq/kg dose group was 0 at all time points. In the 50 kBq/kg and 80 kBq/kg dose groups, there was a consistent decrease in median scores at all post-treatment time points. There was a statistically significant dose response in change from baseline at Weeks 4, 7, and 10 and close to significant at Week 13.
- Median changes in pain function interference index were close to zero at all time points after treatment in the 25 kBq/kg and 50 kBq/kg dose groups but showed a decrease at most time points in the 80 kBq/kg dose group. There was a statistically significant dose response in change from baseline at Week 19.
- The median change in BPI item 5 (pain relief) was close to zero at all times points in all dose groups.

Subjects with pain at baseline:

In the sub-group of the Per-protocol Set with a value of at least 2 on BPI item 3 at baseline (average pain in last week) who provided data for the pain index (67 subjects), the proportion of responders was consistently higher in the 50 kBq/kg dose group (60 to 75%) compared with either the lower (25 kBq/kg) dose group, (33 to 60%) or the higher (80 kBq/kg) dose group, (48 to 61%). There were fewer subjects with pain at baseline in the 25 kBq/kg and 50 kBq/kg dose groups than in the 80 kBq/kg group. There was no statistically significant dose-response relationship.

In subjects with pain at baseline (diary score greater than 0; 90 of 112 subjects in the Per-protocol Set), median diary pain score decreased from baseline in all dose groups and at most time points. At earlier time points (up to Week 13), the median changes from baseline tended to be somewhat larger in the 50 kBq/kg dose group (-0.29 to -0.86) and the 80 kBq/kg dose group (-0.57 to -1.07) than in the 25 kBq/kg dose group (0.00 to -0.43). At later time points, there was no consistent trend. These data were not analyzed statistically.

Median time to death

The median time to death was 548, 569, and 604 days, in the 25 kBq/kg, 50 kBq/kg, and 80 kBq/kg dose groups, respectively. There was no significant difference between groups in the proportion of subjects who died ($p = 0.31$) or in the time to death ($p = 0.44$).

Results Summary — Safety

Adverse events to Week 24:

- In total, 112 of the 122 subjects (92%) reported at least one AE in the period after the first injection of Alpharadin to Week 24, with a total of 551 AEs being reported. There was some dose response in the proportion of subjects with at least one AE (83%, 95%, and 98%, respectively, in the 25 kBq/kg, 50 kBq/kg, and 80 kBq/kg dose groups, respectively). However, the total number of AEs reported (159, 212, and 180) did not appear related to dose.
- The most commonly affected system organ classes were gastrointestinal, musculoskeletal and connective tissue, and general and administration site (54%, 53%, and 46% subjects overall, respectively). The individual AEs (preferred terms) reported most frequently were bone pain; the gastrointestinal events nausea, diarrhoea, constipation, and vomiting; anaemia, fatigue, and asthenia; and anorexia. None had a relation to dose.
- For diarrhoea and nausea, the onset of the majority of AEs (21 of 31 and 19 of 33, respectively) was between the first and the second injection. For the other most frequently reported AEs, there was no clear relation to dosing.

- Nausea, diarrhoea, and vomiting were generally of short duration (median 2 or 3 days) while constipation, anorexia, and asthenia were persistent (median duration 28 days or longer). For a sizeable proportion of reports of bone pain, anaemia and fatigue, the outcome was "not recovered", "unknown" or missing, and the duration, therefore, not reported. Neither the time of onset nor the duration of commonly reported AEs appeared related to dose group.
- The majority of AEs were considered mild or moderate in intensity. Bone pain was the AE most commonly considered to be severe.
- Overall, one-quarter (145 of 551; 26%) of AEs were considered possibly or probably related to study treatment; 33, 57, and 55, respectively, in the 25 kBq/kg, 50 kBq/kg, and 80 kBq/kg dose groups, respectively. The most frequent AEs considered related to study treatment were diarrhoea, nausea, asthenia, and anaemia. The proportion of subjects reporting nausea and anaemia appeared to be related to the dose of Alpharadin.
- The majority of related AEs were Common Toxicity Criteria (CTC) Grade 1 or 2; two were Grade 4, and 10 were Grade 3. Those considered Grade 3 or 4 were most frequently anaemia/haemoglobin decreased and platelet count decreased.

Long-term safety to Month 24

In the Follow-up Period (Week 24 up to Month 24), only AEs considered related to study treatment were required to be recorded. Just one new AE was reported. There was no evidence of late radiation toxicity (no acute leukaemia, myelodysplastic syndrome, aplastic anemia, primary bone cancer, or other serious incident disease).

Deaths, SAEs, withdrawals due to AEs:

- The outcome of 6 AEs with onset before Week 24 was recorded as death: In 3 subjects treated with 25 kBq/kg (cardiac failure, disease progression, and metastases to liver); in 2 subjects treated with 50 kBq/kg (metastatic squamous cell carcinoma and prostate cancer); and in 1 subject treated with 80 kBq/kg (chest pain). All had an unlikely relation to study medication.
- In total, the death of 83 subjects was reported: 29, 25 and 29, respectively, in the 25 kBq/kg, 50 kBq/kg, and 80 kBq/kg dose groups, respectively. The overwhelming majority (73 [92%] of 79 with a reason recorded; 89%, 92%, and 96%, respectively, in the 25 kBq/kg, 50 kBq/kg, and 80 kBq/kg dose groups) died from prostate cancer. Where recorded, all were considered to have an unlikely relation to study medication.
- Overall, 29 subjects experienced a total of 40 SAEs: 9 (22 %) in the 25 kBq/kg dose group experienced 12 SAEs; 7 (18%) in the 50 kBq/kg dose group experienced 12 SAEs, and 13 (31%) in the 80 kBq/kg dose group experienced 16 SAEs. The most frequently reported SAEs were bone pain (6 events), anaemia, disease progression, prostate cancer (4 events each), and spinal cord compression (3 events). The majority of these events was considered related to the underlying disease. In total, 8 SAEs in 7 subjects were considered by the investigator and/or the Sponsor to be related to Alpharadin; these were similar in nature (bone pain, anaemia, prostate cancer, constipation, and muscular weakness) to those considered unrelated.
- Six subjects withdrew from the study due to AEs, which were serious in 5.

Laboratory tests and other measures of safety:

- The median (and mean) values for total white blood cell, neutrophil, lymphocyte and platelet counts were lower at the first visits after each injection than the values before the injection. The decreases were larger in the 50- and 80 kBq/kg dose groups than in the 25 kBq/kg dose group. After the completion of treatment, values generally returned to close to baseline with no obvious differences between the dose groups. The majority of subjects in all the dose groups had counts within the reference ranges at all time points. While there were isolated cases of white cell, neutrophil, or platelet count reaching CTC

Grade 3 or 4, these did not appear to be associated with dose or occur in association with the period shortly following an injection.

- The median (and mean) haemoglobin levels generally showed a decrease over time from baseline up to Month 24, with the decrease being slightly more pronounced in the highest dose group (80 kBq/kg). A high proportion of subjects in all dose groups had haemoglobin levels below the reference range at all time points, which increased with time in the study up to the final follow-up visit at Month 24. However, the changes from baseline to Month 24 were small. The number of reports of CTC Grade 3 or 4 values increased with dose.
- After the Treatment and Post-treatment Period, median values for PSA increased in all dose groups, especially in the second year (Month 12 to Month 24). There was wide variation within and between groups but no clear pattern with dose. For both bone-ALP and s-CTX-I, values were generally higher throughout the study in the 25 kBq/kg dose group than in the 50 kBq/kg and 80 kBq/kg dose groups. However, median values showed little change during the course of the study.
- There were no changes in biochemistry parameters that gave rise to any safety concern.

Changes in physical examination, performance status, extent of disease, and proportion of subjects with disease progression did not give rise to any safety concerns.

Conclusion(s)

This was a study of three different doses of Alpharadin (radium-223 dichloride) given at 6-weekly intervals (previous studies had been conducted using 4-week intervals). The study achieved its primary objective of demonstrating a statistically significant dose-response for Alpharadin using the proportion of subjects with confirmed PSA response (50% reduction in PSA) as the primary endpoint. Time to confirmed PSA response showed a significant dose relationship, demonstrating an effect on PSA kinetics. The confirmed bone-ALP response rate was greater than the confirmed PSA response rate, and was highly statistically significant, and dose-related, consistent with the mode of action of Alpharadin, specifically targeting bone metastases. Alpharadin (3 doses of up to 80 kBq/kg) was tolerated well; the AE profile was consistent with that expected in subjects with advanced prostate cancer, and there were no clear dose-related AEs. A modest decrease in haemoglobin was observed in all dose groups, which was slightly more pronounced in the highest dose group. Mild reversible reductions in white cell and platelet counts, which were not dose-limiting, were the most apparent treatment-related change.

Publication(s):	Parker CC, Pascoe S, Chodacki A, O'Sullivan JM, Germá JR et al. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (Ra 223) in subjects with bone metastases and castration-resistant prostate cancer. Eur Urol [Internet]. 2013 [cited 2013 May 22];63(2):189-97.		
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