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:	15468 (BC1-09)	NCT01070485 EudraCT number: 2009-012189-30
Study Phase:	IIa	
Official Study Title:	An open-label Phase IIa, non-randomized study of Alpharadin® in breast cancer patients with bone dominant disease no longer considered suitable for endocrine therapy	
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:	A total of 4 doses of 50 kBq/kg body weight of Alpharadin were administered as slow intravenous boluses at intervals of 4 weeks.	
Reference Therapy/Placebo		
Reference Therapy:	None	
Duration of Treatment:	Treatment period started at the first administration of the study drug to 4 weeks after the last administration of study drug (approximately 16 weeks).	
Studied period:	**Date of first subject's first visit:**	26 JAN 2010
	Date of last subject's last visit:	24 JAN 2012
Premature Study Suspension / Termination:	Not applicable	
Substantial Study Protocol Amendments:	Protocol amendment 1, dated 14 APR 2010, described the following changes: • Modification of the primary endpoint: Serum bone-specific alkaline phosphatase (S-bone-ALP) was added as the second primary end point. • Lowering of the urine N-telopeptide of type I collagen (U-NTX-1) value for study entry: As the subject population targeted in this study was required to be on bisphosphonate treatment for at least 3 months before the study entry, U-NTX-1 values at study entry could be low despite clear progression of bone disease; therefore, the U-NTX-1 value required at study entry was reduced from 50 to 20 nmol/mmol creatinine. • Clarification of the schedule of assessments: Time windows were allowed for some assessments or visits; visit study days/weeks were corrected to have exactly 2 weeks between each visit during the treatment phase; measurement of biological markers and circulating tumor cells was moved from screening to pre-dose so as to be done as close as possible to the first administration of the study drug; the timing of measurement of U-NTX-1 level at study entry was clarified.	

	• The post-infusion Eastern Cooperative Oncology Group (ECOG) performace status and vital signs assessments were cancelled as they were considered unnecessary. • Administration of bisphosphonates: Available data show that there is no interaction between Alpharadin and bisphosphonates when administrated at least 2 hours apart; this time window was added to the protocol. • The safety follow-up period was harmonized to 28 days throughout the protocol. • Cancer antigen (CA 15.3) analysis: This was to be analyzed locally at each site, not centrally as initially planned. • Bone markers were measured additionally at follow-up visits at 6, 9, and 12 months. • The volume of the blood to be withdrawn was updated. Protocol amendment 2, dated 24 AUG 2010, described the following additional changes: • Removal of the inclusion criterion related to U-NTX-1 value: Even though the U-NTX-1 value required at study entry was reduced in protocol amendment 1, subjects were progressing with bone metastases with even lower values. To allow otherwise eligible subjects to be included in the study, U-NTX-1 was not used as a study entry criterion. • Inclusion of subjects with visceral metastases: Approximately 20% of subjects with progression of bone metastases also had visceral metastases and were excluded (by exclusion criterion 6). Protocol amendment 2 permitted inclusion of these subjects if treatment of their visceral metastases was not initiated, delayed, not wanted by the subject, and they were not being considered for chemotherapy within the next 6 months. • Inclusion of subjects not being treated with bisphosphonate: Subjects who were not being treated with bisphosphonates were permitted to be included in the study, if such treatment was not planned to start during the treatment period.
Study Centre(s):	The study was conducted at four sites in Europe: one in the United Kingdom, two in Belgium, and one in Norway.
Methodology:	In this exploratory study, each subject underwent a Pre-treatment (screening) Period, a 16-week study Treatment Period, and a Follow-up Period upto 12 months after the first administration of the study drug. The eligibility of the subjects was evaluated in the Pre-treatment Period. Subjects underwent screening and baseline assessments after written informed consent was obtained. The treatment period was approximately 16 weeks from the first administration of the study drug to 4 weeks after the last administration of the study drug. During this period, the subject visited the study site at regular intervals and received 4 administrations of the study drug at 4 week intervals on an outpatient basis. The initial follow-up evaluation took place at least 4 weeks after the last administration of the study drug including early termination. During the Follow-up Period, the subject's visits were timed at 3 months intervals up to 12 months after the first administration of the study drug. During these visits, safety and efficacy assessments were done.

Indication/ Main Inclusion Criteria:	Indication: Breast cancer patients with bone dominant disease no longer considered suitable for endocrine therapy Main inclusion criteria: Female subjects: • who were either post-menopausal (cessation of menses for more than 1 year) or surgically sterile (had a documented bilateral oophorectomy and/or documented hysterectomy) or in therapy-induced premature menopause with luteinizing hormone-releasing hormone (LHRH) agonists. If of childbearing potential, the result of a urine human chorionic gonadotropin pregnancy test, performed on the same day as and with the result known before the study drug administration, was required to be negative • with histological or cytological evidence of primary breast cancer • with bone-dominant disease (with or without metastases in soft tissue, lymph nodes and/or skin) identified with at least one non-irradiated bone metastasis on planar bone scintigraphy/single-photon emission computed tomography (SPECT) confirmed by radiographs or computed tomography (CT) within the previous 12 weeks • who had unequivocally progressed on endocrine therapy, and further benefit from endocrine therapy was considered unlikely (progression was required to be documented based on imaging and/or other clinically relevant information) • who had been on bisphosphonate therapy for at least 3 months prior to treatment start and no change to bisphosphonate therapy was expected during the treatment phase of the study, or subjects who were not being treated with bisphosphonates, and such treatment was not planned to be started during the treatment period • with latest endocrine therapy stopped at least 2 weeks prior to treatment start • with ECOG performance status 0–2 • with life expectancy ≥ 6 months • who fulfilled the following laboratory requirements: ➢ White blood cell (WBC) count ≥ 3000/mm^3 ➢ Absolute neutrophil count (ANC) ≥ 1500/mm^3 ➢ Platelet count ≥ 100,000/mm^3 ➢ Hemoglobin ≥ 9 g/dL ➢ Bilirubin ≤ 2.0 mg/dL ➢ Aspartate aminotransferase (AST) and alaline aminotransferase (ALT) ≤ 3 times the upper institutional limit of the normal range ➢ Serum creatinine ≤ 2.0 mg/dL
Study Objectives:	**Primary:** To investigate if multiple intravenous injections of Alpharadin have any clinically relevant effect on bone markers in breast cancer subjects with bone-dominant disease who have progressed on endocrine therapy and are no longer considered suitable for endocrine therapy.

	Secondary: • To evaluate the safety of multiple intravenous injections of Alpharadin • To evaluate potential benefit, palliative, and/or anti-tumor effect of Alpharadin • To evaluate long-term radiation toxicity **Other :** Exploratory objectives • To determine the metabolic effects on bone metastases as a result of Alpharadin treatment • To determine the change in the number of circulating tumor cells as a result of Alpharadin treatment
Evaluation Criteria:	**Efficacy (Primary):** Changes in bone markers, including urine levels of U-NTX-1, given as ratio to creatinine and S-bone-ALP, from baseline to end of treatment (at 16 weeks) **Efficacy (Secondary):** • Other biochemical markers of bone turnover/other timepoints: ➢ Urine: U-NTX-1 and C-telopeptide of Type 1 collagen (U-CTX-1), given as ratio to creatinine ➢ Serum: S-bone-ALP, procollagen of type 1 N-propeptide (S-P1NP) and C-telopeptide of Type 1 collagen generated by matrix metalloproteinases (S-ICTP) • Pain (Brief pain inventory [BPI] short version) • CA 15.3 • ECOG performance status • Time to progression of bone disease **Safety:** All safety data were collected and evaluated, including: • Adverse events (AEs) • Changes in clinical safety laboratory variables: serum biochemistry and hematology • Changes in vital signs (systolic/diastolic blood pressure, respiratory rate, heart rate, and body temperature) • Changes in physical examination • Long-term radiation toxicity, such as new primary cancers and bone marrow changes (acute myelogenous leukemia, myelodysplastic syndrome, and aplastic anemia)
	Other: Exploratory criteria: • Fluorine-18-fluorodeoxyglucose positron emission tomography ([^{18}F] FDG PET) for metabolic changes in the tumor • Circulating tumor cells
Statistical Methods:	**Efficacy (Primary):** Descriptive statistics were used to present the results for each parameter. For each parameter, the distribution of values for change from baseline was checked. If this followed a normal distribution, the

	data were analyzed using repeated measures analysis of covariance (ANCOVA) with change from baseline as the response variable, baseline value as covariate, and study week, extent of disease (EOD), ECOG, baseline value for FDG PET/CT (tumor seen/not seen) as independent variables. If the distribution was skewed, appropriate non-parametric procedures were applied. Since values at baseline, Week 9, and Week 17 were correlated for each subject, the data were analyzed as dependent samples when applying a non-parametric procedure. **Efficacy (Secondary):** Descriptive statistics was used to present the results for each parameter. **Safety:** All safety data were listed and presented using standard summary statistics. The analysis population was the safety/intent to treat (ITT) population. **Other:** Descriptive statistics were used to present the results for each parameter.
Number of Subjects	Approximately 20 subjects were planned to be enrolled, and 23 subjects were enrolled. Of the enrolled subjects, 23 were treated, 15 completed treatment, and 10 completed follow-up. All subjects were included in both the safety and efficacy analyses.

Study Results

Results Summary — Subject Disposition and Baseline

Of the 23 subjects enrolled in the study, 8 subjects did not complete the treatment. The most frequent reason for not completing treatment was disease progression (6 subjects); in addition, 1 died (unrelated) and 1 gave another reason (distance to travel). Of the 15 subjects who completed treatment, 5 did not complete all the follow-up visits. Reasons for not completing these visits were death (progressive breast cancer; unrelated), consent withdrawn (3 subjects), and "other" (2 subjects; 1 due to ill health and 1 missed a visit due to hospital admission with disease progression).

The mean age of all the 23 female subjects was 59.6 ± 10.4 years; mean weight was 65.2 ± 11.2 kg, and mean body mass index was 24.5 ± 4.3 kg/m^2.

Breast cancer had been diagnosed a mean of 10.2 ± 6.52 years ago (range: 1.8-27.8). The majority (14 subjects, 61%) was ductal with 7 (30%) being lobular and 2 (9%) being other. Metastases had first been diagnosed a mean of 4.2 ± 2.85 years ago (range: 1.0-10.6). All subjects had evidence of progression, with the most recent progression being within 17 weeks (mean 7.7 ± 4.33 weeks).

The extent of disease was found to be 3 (more than 20 lesions) in 13 subjects (57%) and 4 (superscan) in 3 subjects (13%); 5 (22%) subjects had extent of disease 2 (6 to 20 metastatic sites), and 2 (9%) subjects had extent of disease 1 (fewer than 6 metastatic sites). Almost all subjects had bone metastases in the pelvis (23 subjects, 100%), vertebral column (22 subjects, 96%), and thorax (19 subjects, 83%), with smaller numbers having metastases in each limb.

Twenty subjects (87%) had FDG PET/CT scans at screening; 8 subjects had chest, abdominal, and pelvic CT or MRI as well as, or instead of, FDG PET/CT. Based on the results from both forms of imaging, 5 subjects had evidence of lymph node metastases and two had evidence of visceral lung metastases. One subject has a deviation recorded because of these lung metastases; in another subject, the metastases were described as not unequivocal and it was not considered that this subject had violated exclusion criterion 6.

Five subjects (22%) had biochemical evidence of progression (elevated CA 15.3 levels). All subjects were ECOG grade 0 (11 subjects; 48 %) or 1 (12 subjects; 52 %) at baseline.

All subjects had received prior/concomitant treatment for breast cancer with bisphosphonates and radiotherapy. A total of 22 subjects (96%) had received hormone therapy or LHRH agonist, 20 subjects (87%) received chemotherapy, and 16 subjects (70%) underwent surgery. Smaller numbers of subjects had received other types of treatment. At study entry, 22 subjects (96%) were treated with bisphosphonate.

Results Summary — Efficacy

Primary efficacy endpoints:

U-NTX-1 corrected for creatinine:

- The overall pattern was a general reduction over the treatment period, with some increase thereafter, with the mean/median returning essentially to baseline by the 12-month time point. Some subjects showed a rapid response, with 7 subjects (30%) with at least a 30% response at the first measurement time point immediately before the second administration of the study drug (Week 5), including 1 subject (4%) with a 50% response. The greatest response rate was observed at the end of treatment, Week 17, when 9 subjects (39%) had at least a 30% response including 5 subjects (22%) with a 50% response. At the 12-month follow-up, 5 subjects (22%) continued to have at least a 30% response, including 2 subjects (9%) with a 50% response.
- In the formal analysis of the primary endpoint over all subjects, the median change in U-NTX-1 from baseline to the end of treatment (Week 17) was −10.1 nmol bone collagen equivalents (BCE)/mmol creatinine (p = 0.0124; −32.8%).
- Pre-specified sub-group analyses indicated that, in general, subjects with the highest baseline values had a greater percentage response (<20 BCE/mmol creatinine: −5%: 20 to 50 BCE/mmol creatinine: −28%;>50 nmol BCE/mMol creatinine: −58%). Each subgroup contained relatively few subjects (3–8), and there was a considerable variability.

S-bone-ALP:

- Changes in S-bone-ALP showed a similar pattern to U-NTX-1. Some subjects showed a rapid response with 8 subjects (31%) with at least a 30% response at the first measurement time point, immediately before the second administration of the study drug, including 3 subjects (13%) with a 50% response. The greatest response rate was observed at the end of treatment, Week 17, when 12 subjects (52%) had at least a 30% response including 8 subjects (35%) with a 50% response. At the 12-month follow-up, 7 subjects (30%) continued to have at least a 30% response, including 5 subjects (22%) with a 50% response.
- In the formal analysis of the primary end point over all subjects, the median change from baseline to the end of treatment (Week 17) was −16.7 ng/mL (p = 0.0045; −42.0%).

Secondary efficacy endpoints:

Other bone markers:

- In general, changes in U-CTX-1, S-P1NP, and S-total-ALP showed a similar pattern to changes in U-NTX-1 and S-bone-ALP. S-ICTP showed no consistent pattern of change during the study.

Pain:

- The median observed change in BPI pain severity index mean across all time points was a small reduction (−0.25 to −1.25). However, statistical analysis of change from baseline at Week 17 for BPI pain severity index mean showed a mean value of −0.6284 (95% confidence interval, −1.4441 to 0.1873; p = 0.2359).
- The BPI functional interference index mean and sum decreased over time during the treatment period; statistical analysis at Week 17 for change from baseline in BPI functional interference index mean showed a mean value of -1.0127 (95% confidence interval, −1.8271 to 0.1982; n = 16; p = 0.0310).

Disease progression:

- The number of subjects with the first recorded disease progression after treatment was 1 of 23 subjects at Month 3 (data on disease progression only available for 3 subjects at Month 3), 10 of 23 at Month 6, 3 of 23 at Month 9, and 2 of 23 at Month 12. Five of 23 subjects did not show any disease progression during the study period, and 2 subjects discontinued the follow-up.

Other secondary end points: There was no consistent trend in CA 15.3 or ECOG performance status values.

Results Summary — Safety

Treatment-emergent adverse events:

- The majority (20 subjects, 87%) of subjects reported at least one treatment-emergent AE (hereafter referred to as AE); in total, 151 AEs were reported. The most frequently reported individual preferred terms were nausea (20 events in 10 subjects), anorexia (10 events in 6 subjects), diarrhea (9 events in 8 subjects), fatigue (9 events in 5 subjects), vomiting (8 events in 6 subjects), constipation (6 events in 5 subjects), and bone pain (6 events in 4 subjects).
- Approximately half of the AEs (54%; 81 of 151 AEs) were considered possibly or probably related to Alpharadin. The most frequently reported individual adverse drug reactions (ADRs) were similar to the most frequent AEs: nausea (10 subjects); diarrhea (8 subjects); anorexia, fatigue, and vomiting (5 subjects each); and constipation and bone pain (3 subjects each).
- Most AEs were Common Toxicity Criteria (CTC) grade 1 or 2. Overall, 17 AEs in 5 subjects were CTC grade > 3 or severe in intensity. There was no particular pattern to these events, bone pain being the only one reported by more than one subject. Whilst a relation to treatment was considered possible for some other severe AEs, there was no pattern to indicate concern.
- Almost all AEs were manageable with no treatment (93 AEs) or with medication (51 AEs); 7 AEs required other management (procedure or other).

Deaths, serious AEs, and withdrawals due to AEs:

- In total, 3 AEs in three subjects were considered serious (1 fatal, 2 resulting in admission to hospital). None was considered related to Alpharadin administration, and the nature of these events (death due to heart failure; hospitalization for depression; hospitalization for cold [nasopharyngitis]) is consistent with the events expected in this subject population.
- One additional subject died during follow-up due to disease progression that, in accordance with the protocol, was not reported as an AE.
- No other AE resulted in treatment delay or discontinuation of treatment.

Laboratory tests and other measures of safety:

- In most subjects, the total white cell, absolute neutrophil, and platelet counts fell after each dose with a nadir in the sample 3 weeks after Alpharadin injection followed by recovery before the next dose.
- A high proportion of subjects had hemoglobin and lymphocyte counts below the reference range at baseline. Mean values for hemoglobin and lymphocyte count generally decreased further during the treatment and follow-up periods.

- Across all hematology parameters, the majority of values below the reference range was CTC Grade 1, with few that were Grade 2 and only isolated Grade 3 values. Many subjects had baseline platelet counts that were above the reference range, and these subjects tended to decrease into the reference range rather than below it.
- Mean and median values for total ALP generally decreased over time during the study with a number of subjects shifting from above the reference range to within the reference range, especially during the treatment period; however, there was wide variability.
- Review of other biochemistry results showed no substantial trends with time. A few subjects shifted from within to above the reference range for ALT and γ-glutamyl-transpeptidase (γGT); the increases in γGT were predominantly during the follow-up period. Almost one-third (7 subjects, 30.4%) had raised AST values on entry to the study, and there was no pattern of change thereafter. CTC grades for peak values for bilirubin, AST, and ALT during the treatment period were normal or Grade 1. There were isolated higher grades for γGT and creatinine.
- There was no pattern of change in vital sign measurements.
- There was no evidence of long-term toxicity.

Results Summary — Other

Exploratory endpoints:

- [^{18}F] FDG PET for metabolic changes in the tumor: One-third of the osteoblastic (target) lesions showed a significant metabolic decrease after two injections of Alpharadin (32.3% response rate at Week 9) that persisted after 4 injections of Alpharadin (41.5% response rate at Week 17). Most of the lesions analyzed showed stable disease; many of these lesions decreased in intensity, but with less than 25% reduction of maximum standardized uptake value (SUVmax) from baseline which was the cutoff for significant metabolic response.
- Circulating tumor cells: Around one-third to one-half subjects with evaluable samples were positive at each time point with no relation to treatment or duration of treatment.

Conclusion(s)

This study showed that 4 intravenous administrations of Alpharadin, 50 kBq/kg, at 4 weeks interval, were associated with statistically significant reductions in U-NTX-1 and S-bone-ALP at the end of treatment in breast cancer subjects with bone-dominant disease who have progressed on endocrine therapy and are no longer considered suitable for endocrine therapy. Whilst there was no control group, study subjects were selected because of the presence of progressive disease; in this population, a decrease over time is suggestive of a positive effect of treatment. There were no unexpected safety findings. Minor reversible hematological toxicity that was not dose-limiting was observed as reported in previous studies with Alpharadin.

Publication(s):	Coleman R, Flamen P, Naume B, Jerusalem G, Garcia C, Piccart M, et al. An open-label, phase IIa, non-randomized study of radium-223 in breast cancer patients with bone-dominant disease no longer considered suitable for endocrine therapy. Poster session presented at: 34th Annual CTRC-AACR San Antonio Breast Cancer Symposium; 2011 Dec 6-10, San Antonio, TX. Flamen P, Garcia C, Piccart M, Coleman R, Naume B, Jerusalem G, Aksnes A, etal. "[^{18}F] FDG PET: Changes in uptake as a method to assess radium-223 dichloride (Ra-223) response in bone metastases of breast cancer patients with bone-dominant disease." SNM's 60th Annual Meeting, June 8-12, 2013, Vancouver, British Columbia.

Date Created or Date Last Updated	15 NOV 2013	**Date of Clinical Study Report:**	04 DEC 2012