Title: An Observation, Open Label Study of Alpharadin (Radium 223) in Patients with Castrate Resistant Prostate Cancer Bone Metastases

Study Drug: Ra-223 dichloride (BAY 88-8223)

Supporter: Bayer

Principal Investigator:
John C. Araujo MD, PhD
University of Texas MD Anderson Cancer
1155 Pressler Drive, Unit 1374
Houston TX 77030
Phone: (713) 792-2830
Fax: (713) 745-1625
Email:johna@mdanderson.org

Co-Principal Investigator:
Eric M. Rohren, M.D. Ph.D.
Associate Professor
Section Chief, Positron Emission Tomography
Department of Nuclear Medicine
Department of Diagnostic Radiology
University of Texas MD Anderson Cancer Center
PO Box 301402, Unit 1483
Houston, TX 77230-1402
Phone: (713) 792-6345
Email: Eric.Rohren@mdanderson.org

1. Introduction

1.1 Hormone-refractory Prostate Cancer

Prostate cancer has high global incidence and mortality. Approximately one in every nine men in North America will be diagnosed with prostate cancer during his lifetime. It is the most common malignancy and the second most common cause of cancer death in North American males. Worldwide, prostate cancer ranks third in cancer incidence and sixth in cancer mortality among men (1).

The course of prostate cancer from diagnosis to death is categorized as a series of clinical states defined by the extent of disease, hormonal status, and absence or presence of detectable metastases on an imaging study. The states are localized disease, rising prostate specific antigen (PSA) after local therapy with radiation therapy or surgery, advanced disease with clinical metastases that initially respond to androgen ablation therapy, and advanced disease that progresses in the presence of androgen deprivation. PSA is a widely used marker of disease progression and response to treatment changes in PSA foretell subsequent changes in radiographic evidence of metastases. The states are recognized by patients and physicians and allow a clear definition of therapeutic objectives and outcomes.

1.2 Background

Advanced Prostate Cancer is associated with prostate cancer-specific mortality and much of the morbidity of the disease. The most common site of metastasis is to bone with 80% of patients dying from the disease having bone metastasis. Skeletal metastasis may result in bone pain, fractures and bone marrow failure. Vertebral involvement may create even more morbidity from spinal cord compression, which if left untreated may result in paralysis.

The androgen receptor (AR) is the primary oncogenic driver of prostate cancer, and the first line of therapy of advanced disease is androgen deprivation, historically by surgical orchiectomy and more commonly, by suppression of the pituitary-gonadal axis with luteinizing hormone releasing hormone (LHRH) analogues. Second line hormonal therapy, by targeting the androgen receptor, has shown a tumor response in less than half of castrate patients. This response is not durable, with median duration of response approximating 7 months. (2) When prostate cancer develops resistance to castration and anti-androgen combinations, a decrease in PSA may be obtained by withdrawing anti-androgen therapy. The withdrawal response rate, however, is no higher and the duration of response even shorter than other second-line hormonal therapies.

After the failure of hormonal therapies, chemotherapy may palliate the symptoms of prostate cancer for those patients who can tolerate the side effects. Docetaxel confers a survival advantage for patients with hormone-refractory prostate cancer, with a median survival of 18 months. Nonetheless, current treatment for advanced prostate cancer is not curative and the

optimal time of administration of chemotherapy remains under active study. Newer agents include Provenge (Sipuleucel-T) a vaccine made from the patient's own cells primed to the prostate specific membrane antigen and re-administered to the patient. As well Abiraterone acetate a CYP17 lyase inhibitor has been shown to increase overall survival in the post chemotherapy setting. In addition Xtandi another androgen receptor blocking agent is available in the post- docetaxel setting.

Xofigo (radium 223) was recently approved in the metastatic castrate resistant prostate cancer patient with symptomatic bone metastasis. In the phase III study time to first SRE, overall survival in the xofigo arm was improved as well, time to total ALP progression, time to PSA progression and a total alkaline phosphatase response was statistically significantly longer in the radium-223 chloride group compared to placebo (see below for statistical details).

In summary, the current natural history of advanced prostate cancer is comprised of one to several years of response to androgen deprivation, several months of response to secondary hormonal therapies, and subsequently cytotoxic chemotherapy for a remaining median survival time of less than two years. There is a medical need to extend the rate and duration of response for chemotherapy while understanding pathways that confer sensitivity or resistance in individualized patients.

1.3 Rationale of the study

Based upon the Radium 223, Alpharadin, phase III trial which has been shown to not only palliate pain but also shown to increase overall survival as compared to placebo (median OS 14.9 months versus 11.3 months) in CRPC without decreases in PSA we propose this study to further understand the mechanism of Radium-223 and its effects within the tumor microenvironment in bone.

These observations outlined above on changes in alkaline phosphatase without significant decreases in PSA are consistent with the hypothesis that targeting the bone microenvironment (osteoblast and/or osteoclast) is implicated in CRPC progression and provides rationale for determining stromal-tumor interactions when exposed to alpharadin.

1.3.1 Pharmacokinetics / pharmacodynamics

Pharmacodynamics within the tumor microenvironment will be determined through sampling of the bone marrow biopsy and aspirates as well as serum/plasma. Please see below for details.

No pharmacokinetics will be performed.

1.4 Ra-223 dichloride

Mechanism of Action
Radium-223 dichloride is a therapeutic alpha particle-emitting pharmaceutical with targeted anti-tumor effect on bone metastases. Ra-223 dichloride mimics calcium and selectively targets bone, specifically areas of bone metastases, by forming complexes with the bone mineral hydroxyapatite. The high linear energy transfer of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in a potent and localized anti-tumor effect. The alpha particle range from radium-223 is less than 100 micrometers (less than 10 cell diameters) which minimizes damage to the surrounding normal tissue.

Preclinical
In single and repeated dose toxicity studies in rats, the main findings were reduced body weight gain, hematological changes, reduced serum alkaline phosphatase and microscopic findings in the bone marrow (depletion of hematopoietic cells, fibrosis), spleen (secondary extra-medullary hematopoiesis) and bone (depletion of osteocytes, osteoblasts, osteoclasts, fibro-osseous lesions, disruption/disorganization of the physis/growth line). These findings were related to radiation-induced impairment of hematopoiesis and a reduction of osteogenesis and occurred beginning in the dose range of 20 (0.00056 mCi) – 80 kBq (0.0022 mCi) per kg body weight, with the exception of body weight decreases.

Dose-limiting myelotoxicity was seen in dogs after single administration of 450 kBq (0.012 mCi) Ra-223 dichloride per kg body weight (9 times the clinically recommended dose). Osteosarcomas, a known effect of bone-seeking radionuclides, were observed at clinically relevant doses in rats 7 – 12 months after start of treatment. Osteosarcomas were not observed in dog studies. The presence of neoplastic changes, other than osteosarcomas, was also reported in the longer term (12 to 15 months) rat toxicity studies. Due to its mode of action, and as seen with conventional radiotherapy and other radiotherapeutics, radium-223 dichloride may have the potential to induce secondary malignancies. No case of osteosarcoma has been reported in clinical studies with Ra-223 dichloride. The risk for patients to develop osteosarcomas with exposure to Ra-223 dichloride is unknown at present

Studies on reproductive and developmental toxicity have not been performed. Since Ra-223 dichloride binds to bone, the potential risk for toxic effects in the male gonads in cancer patients with castration-resistant prostate cancer is very low, but cannot be excluded. Studies on the mutagenic and carcinogenic potential of Ra-223 dichloride have not been performed.

No histological changes were observed in organs involved in the excretion of Ra-223 dichloride. No significant effects were seen on vital organ systems, i.e. cardiovascular (dog), respiratory or

central nervous systems (rat), after single dose administration of 450 to 1000 kBq (0.012 to 0.027 mCi) per kg body weight (9 (dog) to 20 (rat) times the clinically recommended dose.

Clinical Experience Summary

The clinical development of Ra-223 dichloride includes phase I and phase II studies in prostate cancer patients with bone metastases. The results of these completed studies indicated that safety and tolerability of Ra-223 dichloride in CRPC/HRPC patients with bone metastases was well tolerated, and that there was evidence of dose related efficacy against bone markers and other markers of disease. In addition there was an effect on median overall survival in a Phase II (BC1-02) placebo-controlled study. These studies enabled the initiation of the Phase III ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) study.

The clinical safety and efficacy of Ra-223 dichloride have been evaluated in a double-blind, randomized, multiple dose, phase III multicenter study (ALSYMPCA) in castration-resistant prostate cancer patients with bone metastases. The primary efficacy endpoint was Overall Survival (OS).

At the cut-off date of the pre-planned interim analysis, a total of 809 patients were randomized 2:1 to receive Ra-223 dichloride 50 kBq (0.0014 mCi)/kg intravenously every 4 weeks for 6 cycles (N=541) plus best standard of care or matching placebo plus best standard of care (N=268). Best standard of care included (e.g. local external beam radiotherapy, corticosteroids, antiandrogens, estrogens, estramustine or ketoconazole).

An updated descriptive analysis of safety and of OS was performed in 921 randomized patients prior to implementing crossover (i.e. offering patients in the placebo group to receive Ra-223 dichloride treatment).

The results of both, interim and updated analysis, revealed that OS was significantly longer in patients treated with Ra-223 dichloride plus best standard of care compared to patients treated with placebo plus best standard of care. For the updated analysis, an increase in median overall survival of 3.6 months was seen with Ra-223 dichloride plus best standard of care compared to placebo plus best standard of care (HR =0.695 (95% CI 0.581/0.832), median OS 14.9 months versus 11.3 months, respectively).
In the ALSYMPCA study, the results of the interim analysis and the updated analysis showed also a significant improvement in all main secondary endpoints in the Ra-223 dichloride arm compared to the placebo arm:

Time to first SRE (defined as time to EBRT, time to first pathological bone fracture, time to spinal cord compression and time to surgical intervention) was statistically significantly longer in

the radium-223 chloride group compared to placebo (median number of months=15.6 for radium-223 chloride versus 9.8 months for placebo (HR=0.658, 95 CI 0.522–0.830, p= 0.00037).

Time to total ALP progression (defined as ≥ 25% increase compared to baseline/nadir) was statistically significantly longer in the radium-223 chloride group 7.4 months compared to placebo 3.8 months (HR = 0.167, 95% CI 0.129 – 0.217; p= <0.00001).

Time to PSA progression (defined as a ≥ 25% increase and an increase in absolute value of ≥ 2 ng/mL compared to baseline/nadir) was also significantly prolonged in patients receiving Ra-223 dichloride compared to patients receiving placebo (HR = 0.643, 95% CI 0.539,0.768; p = <0.00001).

A total ALP response (defined as a confirmed ≥ 30% or ≥ 50% reduction compared to baseline) at week 12 was observed in higher proportions of subjects who were treated with radium-223 chloride group (47% and 3% respectively) compared to those in the placebo (3% and <1% respectively) group.

Subgroup survival analysis showed a consistent survival benefit for treatment with Ra-223 dichloride, independent of total alkaline phosphatase (ALP), current use of bisphosphonates, prior use of docetaxel and baseline ECOG status. The results from the phase III ALSYMCA study regarding time to external beam radiation therapy (EBRT) for pain relief and fewer patients reporting bone pain as an adverse event in the Ra-223 dichloride group indicate a positive effect on bone pain.

Most common hematologic adverse events all grades were anemia (31.2%), neutropenia (5%) and thrombocytopenia (11.5%). Most common non-hematologic all grades adverse events occurring in more than 15% of patients were: bone pain, diarrhea, nausea, vomiting and constipation.

Table 1 shows adverse reactions occurring in ≥ 1% of patients and for which the rate for Ra-223 dichloride exceeds the rate for placebo.

System/Organ Class Preferred Term	Ra-223 dichloride (n=600)		Placebo (n=301)	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Blood and lymphatic system disorders				
Thrombocytopenia	11.5	6.3	5.6	2
Neutropenia	5	2.2	1	0.7
Leukopenia	4.2	1.3	0.3	0.3
Pancytopenia	2	1.2	0	0
Gastrointestinal disorders				
Diarrhea	25	1.5 (grade 3 only)	15	1.7 (grade 3 only)
Vomiting	18.5	1.7 (grade 3 only)	13.6	2.3 (grade 3 only)
Nausea	35.5	1.7 (grade 3 only)	34.6	1.7 (grade 3 only)
General disorders and administration site conditions				
Injection site reactions (including erythema, pain and swelling)	1.2	0	0	0

*Adverse reactions are identified using MedDRA version 14.1 and graded according to CTCAE version 3.0.

*An additional clinically important adverse reaction observed in less than 1% of <PTN>-treated patients and at a higher incidence than in placebo-treated patients was lymphopenia (0.8% vs. 0.3%).

Secondary Malignant Neoplasms

No cases of radiation-induced cancer have been reported in reported in clinical trials with radium-223 dichloride in follow-up of up to three years. However, the radiation dose resulting from therapeutic exposure may result in higher incidence of cancer (e.g. sarcomas of the bone, or leukemia), mutations and a potential for development of hereditary defects.

2. Study objectives

Primary Objective:

- To identify markers of both predictive and prognostic importance within bone marrow biopsies, aspirates as well as serum in patients with metastatic CRPC to bone, to be treated with the standard 6 doses of Alpharadin.

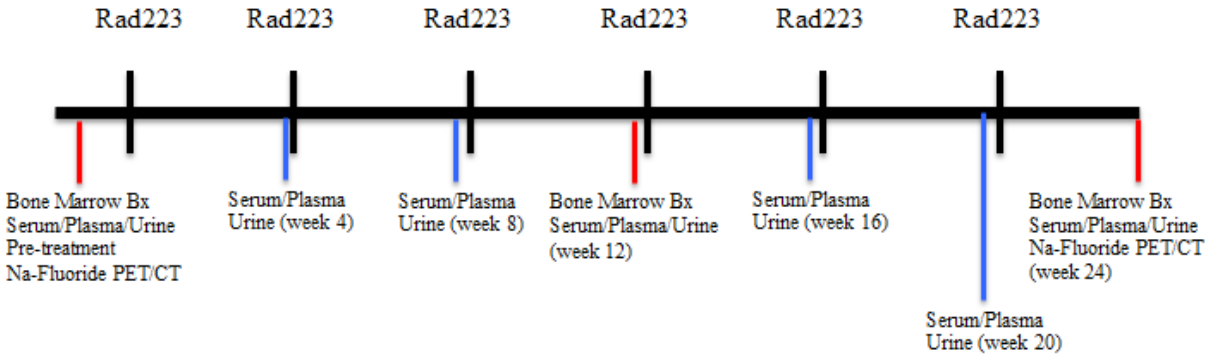
Secondary Objectives:

- Link PSA initial concentration (as defined within PCWG2) to modulation of bone markers, in the blood, urine and bone marrow plasma of study patients
- Estimate the efficacy and PFS by PCWG2 in study patients
- Develop a deeply annotated tissue repository for later hypothesis generating associations
- Correlative studies in prostate cancer patient-derived mouse models to validate predictive and prognostic biomarker associations (SEE APPENDIX E)
- To estimate the overall survival in patients with CRPC

3. Study design

This is an open label study to determine the effect of Alpharadin on the bone marrow microenvironment in patients with CRPC and bone metastases. We will determine the modulation of bone microenvironment as measured by serum, plasma, urine and bone marrow aspirate bone markers. The baseline determination and subsequent assessment of bone-prostate cancer paracrine signaling will be correlated with PSA decline, progression free survival, overall survival and changes in pain indices.

Subjects will be treated with the standard dosing of xofigo (Alpharadin) Ra-223 dichloride 50 kBq (0.0014 mCi)/kg intravenously every 4 weeks for 6 cycles (6 doses total).



For pharmacodynamic effects: tumor/osteoblast/osteoclast along with Ki-67 (proliferation marker), gamma H2AX (DNA double strand breaks),and cleaved PARP. Co-localization by immunohistochemistry for cytokeratin/PSA for tumor cells, BALP for osteoblasts, and TRAP staining for osteoclasts on bone marrow core samples. This will be performed at pre-treatment, week 12 and week 24.

For plasma markers (peripheral blood) indicative of bone formation and degradation this panel will be performed at baseline, week 12, week 16 and week 24: ALP (alkaline phosphatase) BALP* (bone alkaline phosphatase), OPG (osteoprotegrin), RANKL (receptor activator of nuclear factor-B ligand), OPN (osteopontin), OC (osteocalcin), CTX (c-telopeptide-collagen), PINP* (n-terminal propeptide of type 1 procollagen),
Bone secreted factors in the bone marrow aspirate that reflect the status of osteoblasts or osteocytes

1. Alkaline phosphatase--osteoblasts
2. Osteocalcin—both osteoblasts and osteocytes
3. DMP (Dentin matrix acidic phosphoprotein 1)
4. Sclerostin markers of osteocytes

Bone secreted factors that modulate tumor cell activity and tumor cell response to therapies

1. Tenascin—activate integrins
2. Periostin—activate integrins
3. Lumican—active integrins
4. Decorin—binding to EGFR, IGFR, MET, class A scavenger receptor (SR-A)
5. Osteopontin-binding to CD44 and integrins
6. Osteonectin—activate integrins
7. Nidogen-1—activate integrins
8. TGFb-induced protein ig-h3—activate integrins

Urine: NTx (n-terminus cross-linking telopeptide) a marker of osteoclast activity.

We will then assess selected factors in the blood and bone marrow aspirates of the treated patients and will correlate the factors with changes in serum bone specific alkaline phosphatase levels and objective clinical evidence of response to therapy. Our correlative studies will expand on the use of the bone markers outlined above in developed patient-derived xenografts (PDXs) that mimic the heterogeneity of bone-metastatic CRPC (SEE APPENDIX E FOR EXPERIMENTAL APPROACH AND TIMELINE). Together, our clinical and mouse model studies will be performed with the objective of identifying novel factors, early predictors of response to Alpharadin that would guide in the further development and possible earlier use of

Alpharadin or other novel alpha emitters as a therapy for CRPC. These correlations will be conducted using descriptive statistics.

4. Study Population

4.1 Inclusion criteria

1. Histologically proven adenocarcinoma of the prostate with evidence for skeletal metastases on bone scan and/or CT scan.
2. Eastern Cooperative Oncology Group (ECOG) performance status < 2. (Karnofsky Performance Status ≥ 50%)
3. Serum testosterone levels < 50ng/ml
4. Ongoing gonadal androgen deprivation therapy with LHRH analogues or orchiectomy. Patients, who have not had an orchiectomy, must be maintained on standard dosing of LHRH analogue therapy at appropriate frequency for the duration of the study
5. Life expectancy of at least 12 weeks (3 months).
6. Discontinue any steroids prescribed to specifically treat prostate cancer (for e.g as a secondary hormonal manipulation or for cord compression) > 4 weeks prior to study drug. Steroids chronically prescribed for a non-cancer-related illness (e.g. asthma or COPD) that is well controlled with medical management are permissible to an equivalent of <10 mg Prednisone daily. Note: Steroids may be administered during the study as supportive care.
7. Laboratory Requirements:
   a. WBC count > 3,000/µl
   b. Absolute Neutrophil Count (ANC) > 1,500/µl
   c. Hemoglobin ≥ 8.0 g/dL independent of transfusion
   d. Platelet count ≥ 100,000/µL
   e. Serum albumin ≥ 3.0 g/dL
   f. Calculated or measured creatinine clearance > 30 mL/min
8. All acute toxic effects of any prior treatment have resolved to NCI-CTCAE v4.0 Grade 1 or less at the time of signing the Informed Consent Form (ICF).
9. Patient must be willing and able to comply with protocol requirements. All patients must sign an informed consent indicating that they are aware of the investigational nature of this study.
10. Patients must also have signed an authorization for the release of their protected health information.

4.2 Exclusion criteria

1. Treatment with cytotoxic chemotherapy within previous 4 weeks, or failure to recover from AEs due to cytotoxic chemotherapy administered more than 4 weeks previous (however, ongoing neuropathy is permitted)
2. Received systemic therapy with radionuclides (e.g., strontium-89, samarium-153, rhenium-186, or rhenium-188, or Ra-223 dichloride) for the treatment of bony metastases
3. Other malignancy treated within the last 3 years (except non melanoma skin cancer or low-grade superficial bladder cancer)
4. Visceral metastases as assessed by abdominal or pelvic computed tomography (CT) (or other imaging modality)
5. Known brain metastases
6. Lymphadenopathy exceeding 6 cm in short-axis diameter
7. Any size pelvic lymphadenopathy if it is thought to be a contributor to concurrent hydronephrosis.
8. Imminent spinal cord compression based on clinical findings and/or magnetic resonance imaging (MRI). Treatment should be completed for spinal cord compression.
    - Any other serious illness or medical condition, such as but not limited to:
    - Any infection ≥ National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 Grade 2
    - Cardiac failure New York Heart Association (NYHA) III or IV
    - Crohn's disease or ulcerative colitis
    - Bone marrow dysplasia
    - Fecal incontinence
9. Inability to comply with the protocol and/or not willing or not available for follow-up assessments.
10. Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.
11. Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than Ra 223 dichloride.
12. Prior use of Ra-223 dichloride, Strontium or Samarium.
13. Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 4 weeks of trial entry (signing of the informed consent form).
14. Major surgery within 30 days prior to start of study drug.

5. Treatment[s]

Ra-223 dichloride, 50 kBq/kg body weight, will be administered by slow intravenous injection over 1 minute at intervals of every 4 weeks for up to 6 cycles.

5.1 Identity of study treatment

The alpha-pharmaceutical Ra-223 dichloride is a ready-to-use, sterile, non-pyrogenic, clear and colorless aqueous solution of Ra-223 dichloride (223RaCl2) for IV administration. Ra-223 dichloride is an alpha particle emitter with a physical half-life of 11.4 days. The product is isotonic and has a pH of 6.0-8.0. The radioactive concentration at the reference date is 1000 kBq/mL. The product has a pre-calibration of 14 days. When administered on a day other than the reference day, the volume should be corrected according to the physical decay table.

Bayer Healthcare LLC will provide Ra-223 dichloride, which will be manufactured by Algeta's contract manufacturer: Institute for Energy Technology, Isotope laboratories, Kjeller, Norway. The product is produced according to Good Manufacturing Practice (GMP). The product will be delivered in a glass vial, ready-to-use with a certified activity. Ra-223 dichloride is shipped in a lead container and Type A radioactive package according to international transportation guidelines for radioactive materials.

The volume per vial is 6 mL, corresponding to 6 MBq at the calibration day. Ra-223 dichloride has a shelf life of 28 days from production day, when stored at ambient temperature. The shelf life has been demonstrated for temperatures from cold storage (2-8°C) up to 40°C. In addition, it has been shown that the product quality is not jeopardized upon freezing.

All study drugs will be labeled according to the requirements of local law and legislation. For all study drugs, a system of numbering in accordance with all requirements of GMP will be used, ensuring that each dose of study drug can be traced back to the respective bulkware of the ingredients.

5.2 Instructions for use / handling

General Warning
Radium 223 dichloride should be received, used and administered only by authorized persons in designated clinical settings. The receipt, storage, use, transfer and disposal Radium 223 dichloride are subject to the regulations and/or appropriate licenses of the competent official organization. Radium 223dichloride should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

Radiation Protection
The administration of Ra-223 dichloride is associated with potential risks for other persons (e.g. medical staff, care givers and members of the patient's family) from radiation or contamination from spills of body fluids such as urine, feces, or vomit. Therefore, radiation protection

precautions must be taken in accordance with national and local regulations.Radium-223 is primarily an alpha emitter, with a 95.3% fraction of energy emitted as alpha-particles. The fraction emitted as beta-particles is 3.6%, and the fraction emitted as gamma-radiation is 1.1%. The external radiation exposure associated with handling of patient doses is considerably lower in comparison to other radiopharmaceuticals for therapeutic purposes as the administered radioactivity will usually be below 8 MBq (0.216 mCi). In keeping with the As Low As Reasonably Achievable (ALARA) principle, for minimization of radiation exposure, it is recommended to minimize the time spent in radiation areas, to maximize the distance to radiation sources, and to use adequate shielding. Any unused product or materials used in connection with the preparation or administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations.

The gamma radiation associated with the decay of radium-223 and its daughters allows for the radioactivity measurement of Ra-223 dichloride and the detection of contamination with standard instruments.

Dose Calibration
Ra-223 dichloride can be measured in a normal dose calibrator instrument. When written approvals for the use of Ra-223 dichloride from the Radiation Protection Agency for the specific center have been received by the sponsor, a vial of Ra-223 dichloride for technical use will be sent to the study center.

Different clinical study centers possess dose calibrators from various suppliers; thus, the isotope calibration factor may differ from center to center. Consequently, each center must perform the Ra-223 dichloride dial setting on their relevant dose calibrator(s). For dial setting, the clinical study center will receive a sealed vial containing a Ra-223 dichloride solution for calibration only. The vial is identical to the vials used for study treatment. The amount of Ra-223 dichloride in the vial will be stated on the label. Instructions for the dial setting, including the calibration log form, will be enclosed with the dispatch of the calibration sample.

Dosimetry
The absorbed radiation dose calculation was performed based on clinical biodistribution data. Calculations of absorbed doses were performed using OLINDA/EXM (Organ Level INternal Dose Assessment/EXponential Modeling), a software based on the Medical Internal Radiation Dose (MIRD) algorithm, which is widely used for established beta and gamma emitting radionuclides. For radium-223, which is primarily an alpha emitter, additional assumptions were made for the intestine, red marrow and bone/osteogenic cells to provide the best possible absorbed dose calculations for Ra-223 dichloride, considering its observed biodistribution and specific characteristics.

For an administered activity of 3.65 MBq (0.0987 mCi) (50 kBq (0.00135 mCi) per kg body weight to a 73-kg adult), the calculated absorbed doses to the bone (osteogenic cells) is 4.2050 Gy (420.5 rad) and to the red marrow is 0.5066 Gy (50.66 rad). The calculated absorbed doses to the main excretory organs are 0.0265 Gy (2.65 rad) for the small intestine wall, 0.1180 Gy (11.8 rad) for the upper large intestine wall and 0.1696 Gy (16.96 rad) for the lower large intestine wall.

The calculated absorbed doses to other organs are low, e.g. heart wall (0.0063 Gy, 0.63 rad), lung (0.0003 Gy, 0.03 rad), liver (0.0109 Gy, 1.09 rad), kidneys (0.0117 Gy, 1.17 rad), urinary bladder wall (0.0147 Gy, 1.47 rad), testes (0.0003 Gy, 0.03 rad), and spleen (0.0003 Gy, 0.03 rad).

The hematological adverse drug reactions observed in the clinical studies with Ra-223 are much lower in frequency and severity than what could be expected from the calculated absorbed doses to the red marrow. This may be related to spatial distribution of alpha particle radiation resulting in non-uniform radiation dose to the red marrow.

Dose Handling
The Ra-223 dichloride vials must be stored inside their lead container in a secure facility. The study drug should be used within 28 days of production. Ra-223 dichloride is an alpha-pharmaceutical and should be handled by individuals who are qualified by training and experience in the safe handling of radionuclides. One dedicated person and a back-up designee will have responsibility as assigned from the Primary Investigator for handling and storage of Ra-223 dichloride. All administrations of Ra-223 dichloride are based on the certified activity of Ra-223 dichloride at the calibration date.

Dose Calculation
The dosage of Ra-223 dichloride is 50 kBq/kg body weight. The total activity to be injected will be calculated volumetrically using the patient's body weight on the day of injection (kg), the 50 kBq/kg body weight dosage level, and the decay correction factor (DK) to correct for physical decay of Ra-223 dichloride. A table with DK values according to physical decay of the study medication will be provided with each vial of Ra-223 dichloride. The total amount (volume to be drawn into the syringe) to be administered to a patient should be calculated as follows:
Body weight (kg) x50 kBq/kg = volume to be injected (mL)
DK x 1000 kBq/mL
Data regarding activity should be recorded on the appropriate electronic case report form (eCRF) page.

Dose Preparation
Personnel should use appropriate protective clothing and equipment during syringe filling and application to prevent contamination with the radioactive solution (medical gloves / protective glasses). The individual responsible for study drug preparation will draw the correct volume of study drug into a syringe. The size of the syringe should be chosen according to the applied volume to reach the required dosing accuracy. Ra-223 dichloride should not be diluted or mixed with any solutions. Do not store above 40°C (104°F). If the vials have been stored in a refrigerator, they should be left at room temperature for 1 hour prior to use, since cold material should not be injected in a patient. Store Ra-223 dichloride in the original container or equivalent radiation shielding. This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

Dose Administration
Before administration of study drug, the patient must be well hydrated; the patient should be instructed to drink ad libitum. Aseptic technique should be used in the administration of Ra-223 dichloride. The syringe should be handed over to the individual who will perform the injection. The study medication will be administered by slow intravenous injection over 1 minute. After administration, the equipment used in connection with the preparation and administration of drug is to be treated as radioactive waste and should be disposed in accordance with local procedure for the handling of radioactive material.

Drug logistics and Accountability
All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and the instructions given by the clinical supplies department of the Institution and will be inaccessible to unauthorized personnel.

Accountability
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

Destruction and Return
At the end of the study, unused supplies of Ra 223 dichloride should be destroyed according to institutional policies.

Treatment compliance
An adequate record of receipt, distribution, and destruction of all study drugs must be kept in a drug accountability record.

Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol, and to have blood collected for all safety evaluations. At the discretion of the principal investigator, a subject may be discontinued from the trial for non-compliance with follow-up visits or study drug.

6. Dose Modification and Concomitant Medications

Every effort should be made to administer the full dosing regimen of Ra-223 dichloride. Adjustment of dose level is not permitted.

Study visits during the treatment period should occur at 4 weeks intervals (within a window of +/- 7 days). Dosing delays may be instituted under the following circumstances:

Disease progression:

The Investigator should delay cytotoxic chemotherapy, other systemic radioisotope, hemibody external radiotherapy or other investigational drug until the follow-up period. If such treatments have to be given during the treatment period, further study drug administrations must be discontinued. Patients with disease progression may continue treatment at the Investigator's discretion.

Myelosuppression:
Treatment-related changes in hematology parameters may occur.

- If a patient experiences CTCAE v4.03 Grade 3 or 4 neutropenia, thrombocytopenia, or anemia the administration of study drug should be delayed until recovery to Grade 2 or better.
- If a patient experiences CTCAE v4.03 Grade 3 or 4 neutropenia, thrombocytopenia, or anemia lasting > 14 days, further study drug administrations must be discontinued.
- Blood transfusion is acceptable between study drug administrations but not prior to the start of the study. Use of biologic response modifiers, such as G-CSF or GM-CSF, is allowed in the management of acute toxicity.

Gastrointestinal events:

Diarrhea should be treated as per local practice. A further dose of study medication should not be given before diarrhea is recovered to CTCAE v4.03 Grade 2 or baseline levels.
Nausea or vomiting should be treated as per local practice. A further dose of study medication should not be given before nausea or vomiting is recovered to CTCAE v.4.03 Grade 2 or baseline levels.

Spinal Cord Compression:
If the patient experiences spinal cord compression during the treatment period, the patient should be treated for the event, and may receive further study drug administration if adequately recovered.

Surgical Intervention:
If surgery is required, the patient should continue with study treatment, if this is considered safe in the treating Investigator's opinion. The surgeon needs to be notified that the patient has been given radioactive drug, and needs to follow the guidelines for radioactive protection.

Non-pathological fractures:
For traumatic fractures in weight-bearing bones during treatment phase, the study drug administration should be delayed for 2-4 weeks from the time of fracture.

Pathological fractures:
Pathological fractures may occur as the result of either progressive disease or increased physical activity associated with significant pain palliation. Pathologic fractures are to be treated in a manner that attempts to maintain the best functional status and quality of life. Study treatment may continue as planned.

Any Other Toxicity:
Local practice will apply.

6.1 Prior and Concomitant Therapy

All medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator. All medications (including contrast media) taken within 2 weeks prior to the start of the study and during the study must be recorded in the subject's source documentation and in the CRF (including start/stop dates, dose frequency, route of administration, and indication).
Permitted

- Treatment with non-conventional therapies (e.g., herbs [with the exception of St. John's Wart], acupuncture) and vitamin/mineral supplements is acceptable provided that, in the opinion of the investigator, such treatment will not interfere with the trial endpoints.
- Subjects may receive standard of care for any underlying illness.
- In the event of neutropenia, anemia, or thrombocytopenia, subjects may receive appropriate supportive care (e.g., transfusion, biologic response modifiers such as G-CSF or GM-CSF, prophylactic antibiotics, antifungals and/or antivirals, hematopoietic growth factors). This supportive care should not substitute a recommended dose modification.
- Blood transfusions and erythropoietin are allowed during the study period but not within 4 weeks prior to first dose of study drug.
- If surgery is required during study drug treatment, the surgeon needs to be notified that the patient has been treated with a radioactive product and adequate precautions for radioactive protection should be applied during the surgical procedure. The patient should continue with study treatment if considered safe in the treating Investigator's opinion.
- Concomitant treatments for prostate cancer will be recorded in the CRFs. These treatments may include, but are not necessarily limited to: Luteinizing-Hormone-Releasing hormone (LHRH) analogs, surgery, radiation therapy, flutamide, bicalutamide, nilutamide, cyproterone acetate, estramustine, ketoconazole, corticosteroids, estrogens, and abiraterone.

7. Protocol Evaluations

7.1 Screening

Within 21 days prior to enrollment on the study, patients will receive full explanation of the study design and study procedures, provide a written informed consent, and undergo the following screening procedures:

- A medical history including an oncology history,
- Physical exam, including measurement of vital signs, ECOG performance status, height and weight.
- Laboratory studies shall include a CBC w/differential, platelet count, PT, PTT, serum chemistries including albumin, alkaline phosphatase, ALT, AST, calcium, LDH, total bilirubin, creatinine, magnesium, phosphate, calcium, electrolytes (sodium, potassium, chloride, CO_2), PSA, and testosterone.
- A 12-lead electrocardiogram (ECG)
- A bone scan
- Na-Fluoride PET/CT
- A chest x-ray, a computed tomography (CT) scan of the pelvis and abdomen should be performed within 6 weeks prior to start of hormonal ablation.
- Bone Marrow aspirate and bone biopsy as per appendix 1.

7.2 Evaluations During Study

On-study tests/visits that must occur within a defined time frame will have a standing window of allowance that is equal to +/- 7 days.

	Screening	Every 4 weeks	Week 12 only	Safety FU visit (Week 24)	Long-term Follow-up
Medical History	x[a]				
Physical Exam	x[a]	x		x	
Vital Signs[i]	x[a]	x[e]		x	
ECOG PS	x[a]			x	
Weight	x[a]			x	
CBC/ diff. and plt.	x[a]	x[e]		x	
Serum Chemistry	x[a, c]	x[c]		x[c]	
Urinalysis					
PT/PTT	x[a]				
PSA	x[a]	x		x	
Testosterone	x[a]			x	
ECG	X[a]				
ECHO[j]	X[a]				
Chest X-ray	x[b]				
Na-Fluoride PET/CT whole body	x[b]			x	
Bone Scan	x[a]				
Monitor Adverse Events	<----------				---------->
Concomitant Medications	<----------				---------->
Bone marrow asp/bx	x[a]		x	x	
Survival Follow-up					x[d]
Optional Procedures					
Blood for Correlative Studies	x			x	
Urine for Correlative Studies	x			x	

a. Within 21 days of registration

b. Within 6 weeks of registration
c. Serum chemistries including albumin, alkaline phosphatase, ALT, AST, calcium, LDH, total bilirubin, creatinine, magnesium, phosphate, calcium, electrolytes (sodium, potassium, chloride, CO2)

d. Patients will be followed for survival every 6 months after completion of therapy. This may be done by phone call, e-mail, or medical record review.

8. Adverse Event Reporting

8.1 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32)

- Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must

be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

8.2 Reporting of Adverse Events

Adverse Events will be documented according to the Recommended Adverse Event Recording Guidelines for Phase II protocol (see table below).

Recommended Adverse Event Recording Guidelines					
Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III

Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III		Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III		Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III		Phase I Phase II Phase III	Phase I Phase II Phase III

8.3 Reporting Requirements to Supporting Company:

This trial will use the NCI-CTCAE v4.0 criteria for assessment of toxicity and SAE reporting with regard to toxicity grade.

8.3.1 Adverse events

Investigators should refer to the Safety Information section of the current IB for Ra 223 dichloride, including the DCSI (development core safety information), for the expected side effects of Ra 223 dichloride. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions. The IB will be updated if any new relevant safety data are obtained.

Therapeutic monitoring should be performed following dose selection of Ra 223 dichloride in a manner consistent with the local clinical standard of care. In general, subjects should be closely monitored for side effects of all concomitant medications regardless of the path of drug elimination.

All concomitant medications must be recorded in the subject's source documentation. Subjects must be carefully monitored for AEs. This monitoring also includes clinical laboratory tests. Adverse events should be assessed in terms of their seriousness, intensity, and relationship to the study drug, or other chemotherapy/treatment.

8.3.2 Reporting of serious adverse events

Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports to the designated person. An isolated laboratory abnormality that is assigned

grade 4, according to CTC definition, is not reportable as an SAE; unless the investigator assesses that the event meets standard ICH criteria for an SAE. CTC grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria.

All serious adverse events should be reported to Bayer within 24 hours. In the event of such an event, the investigator should refer to the Pharmacovigilance section of the contract for reporting procedures.

The Investigator may report serious adverse drug reactions (SADRs) using the MD Anderson Adverse Event Form.

All reports shall be sent electronically to:

Electronic Mailbox: DrugSafety.GPV.US@bayer.com

Reports for all Bayer products can also be phoned in via our Clinical Communications Dept:

Phone: 1-888-842-2937

8.3.4 Progressive disease

If progressive disease leads to signs and symptoms that meet the criteria for an SAE (i.e., hospitalization, disability, death, or important medical event), the signs and symptoms should be reported as an SAE and not the underlying progressive disease.

Death

If any subject dies during the trial or within 30 days of the end-of-treatment visit, the investigator will inform Bayer and record the cause of death in detail (using the SAE Form) within 24 hours.

9. Withdrawal of subjects from study

Subjects must be withdrawn from the trial (treatment and procedures) for the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Subject is lost to follow-up.
- Death.

Subjects may be withdrawn from the study for the following reasons:

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- The development of a second cancer.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 4.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records.

9.1 Screen Failures/Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been randomized; assigned to treatment/run-in/wash-out; administer at least one dose of study drug.

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see above) is regarded a "screening failure".

9.2 Replacement

No withdrawn subjects will be replaced.

10. Statistical Considerations

10.1 Analysis sets

Full population:

All enrolled patients will be used for demographic reporting and calculations of the numbers of patients able to complete the planned schedule and be evaluable for serum and bone marrow marker studies.

Evaluable for Serum Markers:
All patients who have usable baseline and at least one post-baseline serum draws will be evaluable for analysis of serum markers.

Evaluable for Bone Marrow Markers:
All patients who have usable baseline and at least one post-baseline bone marrow biopsy will be evaluable for analyses of bone marrow markers.

Toxicity:
All patients who receive a bone marrow biopsy will be evaluable for toxicity.

10.2 Variables

Overall survival (OS):
OS will be measured as the number of months from enrollment until death. Patients who are alive at the time of database lock will be censored on the date of last contact.

Progression-free survival (PFS):
PFS will be measured as the number of months from enrollment until progression or death, whichever comes first. Patients who are alive and free of progression at their last response evaluation will be censored on that date. Progression will be defined by the standards set forth within PCWG2.

Demographic variables:
Age at enrollment, race, ethnicity, ECOG status, extent of bone disease (< 6, 6-20, >20)

PD Effects:
Tumor/osteoblast/osteoclast, Ki-67, gamma H2AX, cleaved PRP, cytokeratin/PSA, BALP, and TRAP

Serum biomarkers:
ALP, BALP, APG, RANKL, OPN, OC, CTX, PINP

Bone marrow biomarkers:
Alkaline phosphatase, osteocalcin, DMP, sclerostin, tenascin, periostin, lumican, decorin, osteopontin, osteonectin, nidogen-1, TGFb-induced protein ig-h3.

10.3 Descriptive Statistics

Patient demographics and medical status at study enrollment will be tabulated for all enrolled patients. Descriptive plots and summaries of adverse events (AE), PD measures, as well as

serum and bone marrow biomarkers will be presented. The proportions of patients with at least a 30% increase or decrease in any marker will be presented. AEs will be reported by grade and relationship to study interventions (therapy and blood draws and biopsies all constitute study interventions).

10.4 Markers

Markers will be measured repeatedly over time. Any patient with both baseline and at least 1 later measurement will be included in descriptions of each marker. Patients will also be classified for each marker based on whether the marker decreased by at least 30%, stayed with 30% of baseline, or increased by at least 30%. Currently there is no knowledge of how the planned PD, serum, and bone marrow markers may predict overall survival. Exploratory analyses described below will be performed on the continuous values of the markers, changes, in the markers as continuous measures, and the classification strategy described here.
16.3.3 Survival Analysis.

Overall (OS) and progression-free (PFS) survival will be calculated from the date of study enrollment and will include all enrolled patients. Survival analyses will be performed when 90% of patients have died or 2 years after the last patient has completed treatment, whichever comes first. Plots of all patients and subgroups identified by marker exploration (described below) will be presented using the methods of Kaplan and Meier.

10.5 Primary Objective Exploration

Each marker will be tested individually using a Cox regression model to determine whether it is associated with overall survival. Markers measured on a continuous or ordinal scale will be included with their original units in the model. First, the baseline values will be used to determine if the baseline is associated with survival. Next we will calculate the percent change from baseline and use that as a continuous measure in the model. The ordered category of reduced by 30%, same, or increased by 30% grouping will be used in the model. Finally, all observed values of the marker will be included as a time-varying covariate in the Cox regression model. Since this is an observational study to identify potential usefulness of biomarkers in predicting overall survival, no formal adjustments for multiple testing will be needed for future trial planning. However, for publication, only markers with a significance level of ≤ 0.002 will be considered meaningful in predicting survival. This is based on a Bonferroni correction of approximately 25 markers of interest. Additional regression-tree style partitioning may be performed to identify potentially meaningful cutpoints for combinations of markers. Cutpoints will be examined together with demographic and medical status variables. This will be purely exploratory and will need to be confirmed in an independent data set in a future trial.

10.6 Secondary Objective Analyses

Similar analyses as described for the primary objective will be carried out for progression-free survival as well. Graphical displays including individual biomarkers and progression events will be explored for patterns.

10.7 Planned Interim Analyses

While grade 3 or higher toxicities are rare (~6%) with Alpharadin as therapy for metastatic prostate cancer, it has not been combined with bone marrow biopsies so stopping rules for excessive unexpected toxicities will be implemented in case the treatment has unexpected effects on pain, bleeding, or healing of the biopsy site. A Bayesian sequential monitoring design (Thall et al. 1995 and 1998) will be used to monitor the trial for toxicity. Trial limiting toxicities (TOX) are any grade 3 or higher toxicities at least possibly related to the study drug that occur any time between the first bone marrow biopsy and 30 days after the last treatment is given. The trial will be terminated if Prob(TOX > 0.20 | data) > 0.95. Assuming a prior distribution of TOX for this experimental treatment of ~beta(1,1), pre-defined stopping boundaries corresponding to this probability criterion are provided in the following table. Calculations were performed in Multc Lean 2.1.0 using 0.20 as a constant rate. Following this rule, the trial will be terminated according to the following table once the first 5 patients have enrolled. Operating characteristics for these stopping rules are presented in 10.7.1.

Table 10.7.1: Toxicity Stopping Rules

If there are this many patients (or more) with TOX	3	4	5	6	7	8	9*
Stop the trial if there are this many (or fewer) patients who are evaluable (have TOX or completed the first cycle without TOX)	6	9	13	16	20	24	25*

TOX= any toxicity that is: grade ≥3 AND at least possibly related to study drug AND occurs any time from first bone marrow biopsy up to 30 days after last treatment is given.
Note: that the trial will stop with 25 patients regardless of toxicities. However, if there are 9 or more patients with TOX of the 25, then repeated bone marrow biopsies during Alpharadin therapy will be considered too toxic for future studies.

Table 10.7.2: Operating characteristics for toxicity monitoring

	Stop if Prob{DLT > 0.20 | data} > 0.95		
True Toxicity Rate	Pr(stop early)	Mean Number of Patients	Median (25^{th} %ile, 75^{th} %ile)

0.10	0.02	24.6	25 (25, 25)
0.15	0.08	23.7	25 (25, 25)
0.20	0.21	21.9	25 (25, 25)
0.25	0.38	19.5	25 (12, 25)
0.33	0.68	15.0	13 (6, 25)
0.40	0.87	11.4	5 (8, 16)

10.8 Determination of Sample Size

This is an observational study of a new standard therapy with proven safety and efficacy to identify markers that change with treatment and are associated with overall survival. All findings will be preliminary and will be used to design future trials of scientific determination. No formal sample size criteria have been used. However, with 25 patients, we will have 80% power to detect a hazard ratio (HR) of 1.57 for a continuous biomarker as associated with survival at a 2-sided 5% significance level if the standard deviation of the biomarker is 1.25. With wider spread of the biomarker values, smaller HRs can be detected. For example, if the standard deviation is 1.5, then a HR of 1.45 could similarly be detected as significant.

11. Data and Protocol Management

11.1 Registration Procedure and Data Reporting

All data will be entered to the Department of Genitourinary Medical Oncology Oracle database (GURU). GURU is a password protected database with an audit trail. Data can be collated with a unique GURU identification in order to de-link information. The minimum required fields will be entered to the MDACC required data collection systems (CORe/PDMS). Registration data entry will occur prior to initiation of therapy. All eligibility criteria must be satisfied.Reporting to the supporting agency will follow the contract agreement.

11.2 Clinical Trial Posting

Information related to this study will be posted on www.clinicaltrials.gov before the first patient is enrolled in the study.

11.3 Audit and Inspection

Inspections by regulatory health authority representatives i.e. FDA and IEC(s)/IRB(s) are possible. The investigator should notify Bayer immediately of any such inspection.

12. Publication Policy

Bayer recognizes the right of the investigator to publish results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to Bayer at least thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication or congress presentation. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between Bayer and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties. All relevant aspects regarding data reporting and publication will be part of the contract between Bayer and the investigator/institution
The Principal Investigator should ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

13. Reference

1) Data on file. Bayer HealthCare Pharmaceuticals Wayne, NJ.
2) Miller CE, Finkel AJ. Radium retention in mice after single intravenous injection. Radiat Res. 1965;26(2):269-286.
3) Lloyd RD, Miller SC, Taylor GN, Bruenger FW, Angus W, Jee WS. Comparison of internal emitter radiobiology in animals and humans. Health Phys 1997;72(1):100-10.
4) Henriksen G, Breistøl K, Bruland OS, Fodstad O, Larsen RH. Significant antitumor effect from bone-seeking, alpha-particle-emitting (223)Ra demonstrated in an experimental skeletal metastases model. Cancer Res. 2002;62(11):3120-3125.
5) Henriksen G, Fisher DR, Roeske JC, Bruland OS, Larsen RH. Targeting of osseous sites with alpha-emitting 223Ra: comparison with the beta-emitter 89Sr in mice. J Nucl Med. 2003;44(2):252-259.
6) Parker C. et al. ASCO 2012. Overall Survival Benefit and Safety Profile of Radium-223 Chloride (Alpharadin), A First-in-Class Alpha-Pharmaceutical: Results from a Phase III Randomized Trial (ALSYMPCA) in Patients With Castration-Resistant Prostate Cancer (CRPC) With Bone Metastases
7) Parker C. et al. ICPU 2013. Quality of life (QOL) and updated survival and safety data of radium-223 dichloride in patients with castration-resistant prostate cancer (CRPC) with bone metastases from the phase 3 ALSYMPCA study
8) Sartor O. et al ICPU Safety of cytotoxic chemotherapy following radium-223 dichloride therapy in the phase 3 ALSYMPCA study in patients with castration-resistant prostate cancer (CRPC) with bone metastases
9) Vogelzang N et al. ASCO GU 2013. Updated Analysis of Radium-223 Dichloride Impact on Skeletal-Related Events (SRE) in Patients With Castration-Resistant Prostate Cancer (CRPC) and Bone Metastases From the Phase 3 Randomized Trial (ALSYMPCA).

10) Nilsson S., Sartor O., Bruland Ø., Fang F., Aksnes A-K., Parker C. ASCO GU 2013. Pain Analysis From the Phase 3 Randomized ALSYMPCA Study With Radium-223 Dichloride in Castration-Resistant Prostate Cancer (CRPC) Patients With Bone Metastases.
11) Heinrich et al, EAU 2013, Updated Analysis of Radium-223 Dichloride (Ra-223) Impact on Pain, Skeletal-Related Events (SRE), and Survival From the Phase 3 Randomized Trial (ALSYMPCA) in Patients With Castration-Resistant Prostate Cancer (CRPC) and Bone Metastases