Phase II open, non-randomized trial assessing pain efficacy with Radium-223 in symptomatic metastatic castration-resistant prostate cancer

Prostate Cancer Clinical Trials Consortium, LLC (PCCTC)
PCCTC LOI #: c13-124
Lead Site/Sponsor: Memorial Sloan Kettering Cancer Center

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INVESTIGATOR'S APPROVAL OF PROTOCOL

*Title***:** Phase II open, non-randomized trial assessing pain efficacy with Radium-223 in symptomatic metastatic castration-resistant prostate cancer

Principal Investigator Signature: _____

Principal Investigator Print: _____

Date: _____

SYNOPSIS

Title	Phase II open, non-randomized trial assessing pain efficacy with Radium-223 in symptomatic metastatic castration-resistant prostate cancer
Lead site	Memorial Sloan Kettering Cancer Center
Sponsor	Investigator-initiated
Investigational agent	Radium 223 administered intravenously every 4 weeks for 6 doses at 50 kBq/Kg (55kBq/kg b.w. after implementation of the NIST update).
Phase	II
Target population	Men with symptomatic metastatic castration-resistant prostate cancer.

Inclusion Criteria

- Males aged 18 years of age and above
- Histological or cytological proof of prostate adenocarcinoma
- Castrate serum testosterone level: ≤50 ng/dL (≤1.7 nmol/L)
- Patients who have experienced disease progression despite initial hormonal therapy, either by orchiectomy or by using a GnRH agonist in combination with an anti-androgen, must first progress through anti- androgen withdrawal prior to being eligible. The minimum time frame to document failure of anti-androgen withdrawal will be four weeks. Patients on second-line (or beyond) hormonal maneuvers, and patients who had no PSA decline on combined androgen blockade as first line therapy, need not progress through AAW in order to be eligible.
- Known progressive castration-resistant disease, defined as:
    - Serum PSA progression defined as two consecutive increases in PSA over a previous reference value within 6 months of first treatment, each measurement at least one week apart. Serum PSA at screening ≥ 2 ng/mL

  or

    - Documented appearance of new lesions by bone scintigraphy
- ECOG Performance Status of 0-2 (Appendix A: Performance Status Criteria)
- 2 or more bone metastases demonstrated on bone scintigraphy
- Pain at baseline as measured by a BPI worst pain score average of ≥ 3. The BPI worst pain score average will be based on the worst pain scores completed by the patient in the 7 consecutive pretreatment days. A minimum of 4 days of pain scores must be completed by the patient in the 7 day window in order to

calculate the average worst pain score. The investigator will optimize the subject's pain regimen prior to study entry.

- Normal organ function with acceptable initial laboratory values:
  - WBC $\geq 3 \times 10^9$ /L
  - ANC $\geq 1.5 \times 10^9$ /L
  - Platelets $\geq 100 \times 10^9$ /L
  - Hemoglobin $\geq$ 9.0 g/dL
  - Creatinine < 1.5 x institutional upper limit of normal (ULN)
  - Bilirubin $\leqslant$ 1.5 x ULN
  - AST/ALT $\leqslant$ 2.5 x ULN
  - Albumin > 25 g/L
- All acute toxicities as a result of any prior treatment must have resolved to NCI-CTCAE v4.0 Grade 1 or less at the time of signing the Informed Consent Form (ICF) [**Note:** Ongoing grade 2 neuropathy as a result of treatment with a cytotoxic chemotherapy regimen is permitted]
- Life expectancy of at least 6 months
- Willing and able to provide written informed consent and HIPAA authorization for the release of personal health information

  NOTE: HIPAA authorization may be either included in the informed consent or obtained separately
- Willing and able to comply with the protocol, including follow-up visits, examinations as well as having the ability to self-report pain and fatigue using a Patient Reported Outcome (PRO) instrument
- Willingness to use adequate methods of contraception beginning at the signing of the ICF until at least 30 days after the last dose of study drug

Exclusion Criteria

- Prior exposure to Radium-223
- Received an investigational therapy within the 4 weeks prior to registration, or is scheduled to receive one during the treatment period
- Received a new anti-cancer agent within 4 weeks prior to registration
- Received external beam radiotherapy within 4 weeks prior to registration
- Received systemic therapy with radionuclides (e.g. strontium-89, samarium-153, rhenium-186 or rhenium-188) for the treatment of bone metastases
- Treatment with cytotoxic chemotherapy within 4 weeks prior to registration
- Symptomatic nodal disease, i.e. scrotal, penile or leg edema.

- Visceral metastases (including cerebral metastases) from CRPC (>2 lung and/or liver metastases [size ≥2cm]; Lymphadenopathy exceeding 6 cm in short-axis diameter or any size pelvic lymphadenopathy if it is thought to be a contributor to concurrent hydronephrosis), as assessed by CT, MRI or chest X-ray within the 8 weeks prior to registration.
- Concurrent chemotherapy. Patients may be on other non-chemotherapy anti-cancer treatments, per FDA labeling of Radium-223, provided that these are not changed during the primary pain assessment period
- Major surgery within 30 days prior to registration.
- Imminent spinal cord compression based on clinical findings and/or magnetic resonance imaging (MRI). Treatment should be completed for spinal cord compression.
- Patients with a, "currently active," second malignancy other than non-melanoma skin cancers or non-invasive bladder cancers or other in-situ or non-invasive malignancies. Patients who have completed therapy for a prior malignancy and are free of disease for ≥3 years are eligible.
- 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
- Any other condition which, in the opinion of the Investigator, would make the subject unsuitable for trial participation

Study centers	3 sites in the United States
Start date/Duration	First patients are expected to be enrolled in January 2015. Accrual is estimated to last 1 year with up to 6 months of follow-up after the last patient has been entered.
Expected enrollment	63 patients
Rationale	The dose selected for this agent is (50 kBq (0.00135 mCi) (55kBq (.0015 after NIST update) administered every 4 weeks for 6 doses. This was selected based on prior studies, including the dose used in the randomized, phase III study that demonstrated a 31% reduction in the risk of death in comparison to placebo.
Objectives	**Primary** The primary objective of this study is to determine the effects of pain palliation with

Radium-223.

Secondary

The secondary objectives of this study are:

- To assess the impact of treatment on markers of bone turnover
- To assess the impact of treatment on PSA
- To assess the impact of treatment on time to radiographic progression
- To assess the impact of treatment on quantifiable imaging biomarkers assessing bone metabolism
- To assess the impact of treatment on tiredness
- To assess the toxicity of treatment
- To assess the impact of treatment on pain interference specifically evaluating its affect on general activity and sleep as measured by the BPI
- To assess the impact of treatment on time to pain progression
- To assess the impact of treatment on change in analgesic use

Study design

This is an open, single arm phase II study.

The study will open in three sites in the U.S. Prostate Cancer Clinical Trials Consortium (PCCTC).

This is a two-phase design such that in the first phase, 27 patients will be accrued. If 6 or more patients achieve a pain response (defined as a 30% decline in the BPI worse pain item from baseline to week 8, with a confirmed reduction at week 12 without an escalation of the subjects pain regimen from Step 1 to Step 2 or Step 2 to Step 3 of the WHO analgesic ladder.), then an additional 36 patients will be enrolled. If fewer than 6 patients achieve a pain palliation response, the study will be terminated.

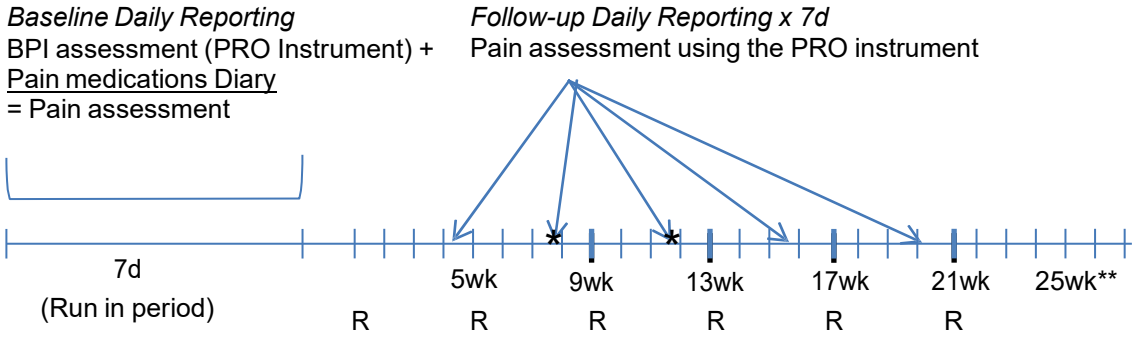
Treatment period: From first intravenous administration of study drug to 4 weeks after the last administration of study drug.

Safety Follow-up Visit: Patients will be evaluated 1 month (±7 days) after they have completed treatment with 6 doses or the patient is prematurely discontinued from treatment.

Follow-up period: Patients will be evaluated every 3 months (± 1 week) until 6 months after the safety follow-up visit for a total of 2 visits.

End of study: Last follow-up visit for the last patient on study.

A schema for study treatment appears below:



*Primary endpoint: Pain response at 8wk confirmed at 12wk
**Pain measured every 12 weeks thereafter
R=Radium-223 50kBq/kg
PRO Instrument

Criteria for evaluation

Primary

Proportion of patients with pain palliation (pain response) at week 8, confirmed at week 12 without an escalation of the subjects pain regimen from Step 1 to Step 2 or Step 2 to Step 3 of the WHO analgesic ladder.

Secondary

- Changes in Bone-ALP
  - Percentage of change from baseline to 12 weeks (or earlier for those who discontinue study therapy)
  - Maximum change (rise or fall) in bone-ALP during the treatment period reported for each patient as a waterfall plot
- Changes in other bone markers:
  - Serum C-telopeptide (sCTX-1)
  - N-terminal propeptide of procollagen type 1 (PINP)
  - Changes in total-ALP will be defined as for bone-ALP above
- Changes in PSA
  - Using Prostate Cancer Working Group 2 (PCWG2) guidelines [1], the percentage of change in PSA from baseline to 12 weeks, as well as the maximum decline in PSA will be reported for each patient using a waterfall plot.
  - Progression, for those patients showing an initial decline in PSA from baseline, is defined as an increase in PSA that is ≥25% and ≥2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend).
  - Progression, for those patients with no decline in PSA from baseline, is defined as an increase in PSA that is ≥25% and ≥2 ng/mL after 12 weeks. Note: PSA progression as such will not lead to study discontinuation
- Time to First Radiographic or Clinical Progression (TTFROCP) based on RECIST version 1.1[2] and PCWG2 definitions[1]

- Radiographic response will also be determined using FDG PET/CT to assess for treatment effect in bone. Section 10.1.2 discusses how response will be assessed.
- Time to pain progression, defined as time until a ≥2 point increase in pain compared to baseline confirmed at least 2 weeks later.
- Change in analgesic use assessed by the WHO analgesic ladder
- Changes in measure of tiredness measured by the worst fatigue item (item #3) from the Brief Fatigue Inventory. (see Appendix E)
- Changes in measures of pain interference as assessed on Brief Pain Inventory. (see Appendix F)
- Evaluate the short and long term toxicity to treatment

Statistical method

Primary Analysis

The primary objective of this phase II study is to determine the effect of Radium-223 on pain improvement for patients with symptomatic metastatic castration-resistant disease. The primary endpoint of the study is a 30% decline in the BPI worst pain item from baseline to week 8, with a confirmed reduction at week 12, without an escalation of the subject's pain regimen from Step 1 to Step 2 or Step 2 to Step 3 of the WHO analgesic ladder. We define this event as a response and propose declaring the treatment effective if the probability of a response in the population exceeds 0.20.

A maximum of 63 patients will be entered onto the study. A two-stage design that differentiates between response rates of 0.20 and 0.35 will be used to assess treatment efficacy. In the first stage of the study 27 patients will be enrolled. If at most 5 patients respond, accrual will be terminated. If at least 6 patients respond, an additional 36 patients will be entered onto the study. At the conclusion of this second stage, if at least 17/63 patients respond, the treatment will be declared effective. The probability of declaring the treatment effective is 0.10 when the response rate in the population is 0.20 and increases to 0.90 when the response rate is 0.35.

Secondary Analysis

Descriptive statistics will be used to report the proportion of patients with various changes in fatigue scores compared to baseline according to the worst fatigue item (Item #3) of the Brief Fatigue Inventory, at weeks 8 and 12. Descriptive statistics will also be used to report the proportion of patients with changes in pain interference scores compared to baseline based on the interference with activities item of the BPI, at weeks 8 and 12.

The time to radiographic progression will be summarized using the cumulative incidence function.

The percent change in PSA and bone turnover markers from baseline to 12 weeks will be summarized with descriptive statistics.

Metabolic response will also be determined using FDG PET/CT to assess for treatment effect in bone.

Safety analysis

Standard safety summaries will be provided for treatment exposure, patient disposition, adverse events leading to discontinuation, serious adverse events, and all

events resulting in death, including those up to 4 weeks after treatment discontinuation. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance.

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Disease Background

Metastatic prostate cancer is characterized by a unique predilection for bone; 80-90% of patients with advanced disease have radiographically detectable osteoblastic metastases. With bone metastases comes significant clinical sequelae including bone pain, fractures, epidural disease and cord compression. Collectively these events can cause significant detriment to patient quality of life. The prevalence of baseline bone pain in contemporary trials of patients with metastatic castration-resistant prostate cancer is estimated between 2-54%[3]; however, there is variability in instruments used to assess pain, many of which have not been validated in this disease and the study populations have varied significantly. Despite the prevalence of bone pain, contemporary clinical trials have not addressed an agent's ability to palliate pain in a fashion that could be used for regulatory approval for this indication.

Establishing pain relief is a regulatory pathway for drug approval in oncology, although the last agent to do so was in 1996 with mitoxantrone/prednisone. Historically, the other agents that are FDA approved for use in palliating painful bone metastases are both beta-emitting bone seeking radiopharmaceuticals, Strontium-89 and Samarium-153 EDTMP. These agents however have been limited for concern for bone marrow toxicity. For this reason, the development of novel alpha emitting radiopharmaceuticals that offer less hematologic toxicity is an appealing strategy.

1.2 Treatment Background

Alpha Emitting Bone Seeking Radionuclide Radium-223 dichloride (Xofigo™)

Radium-223, , is a first in class alpha-emitting radiopharmaceutical that offers substantially less marrow toxicity and has been developed for use in metastatic castration-resistant prostate cancer (mCRPC) patients with bone metastases. It is unique in that the alpha radiation range is limited to less than 100 micrometers and therefore highly localized with less damage to the surrounding marrow. This induces double strand breaks in DNA in contrast to beta-emitters that exert lower energy and induce single strand breaks that may be more amenable to cell repair.

1.2.1 Description

Clinical studies

Based on promising pre-clinical data, Radium-223 was introduced into clinical development in 2001 and has subsequently advanced through the stages of drug development, culminating in a recently completed, international randomized phase III trial (known as the ALSYMPCA trial) that demonstrated a 30% survival advantage in comparison to placebo. The drug is now FDA approved for men with symptomatic mCRPC with bone metastases.[4]

Initial clinical trials (AT1-BC-1) studied 31 patients with bone metastases from breast or prostate cancer and evaluated escalating single doses of 46, 93, 163, 213 and 250 kBq/kg b.w. corresponding to 51, 103, 180, 235, and 276 kBq/kg, respectively, after implementation of NIST update) as well as with multiple doses

(50 kBq/kg at 3 wk intervals x 5 corresponding to 55kBq/kg after implementation of the NIST) or 125 kBq/kg b.w. corresponding to 138kBq/kg after implementation of the NIST at 6 wk intervals x 2). Decreases in total alkaline phosphatase were observed as well as preliminary pain efficacy.[5]

A second clinical trial of 64 patients treated with either 4 doses of 50 kBq/kq (to 55kBq/kg after implementation of the NIST)q 4 weeks or placebo confirmed significant decline in alkaline phosphatase, as well as declines in PSA and an increase in survival from 46 to 65 weeks.[6] In study BC1-03 of 100 patients that received single doses of 5, 25, 50 or 100 kBq/kg (corresponding to 6, 28, 55, and 110 kBq/kg after implementation of NIST update] an ad-hoc analyses of pain palliative response was performed and found to demonstrate pain relief at 8 weeks in 40%, 63%, 56%, and 71%, respectively. There was suggestion that pain relief was improved at higher dose levels. However, the measures utilized to assess pain were not standard and therefore require prospective evaluation with a priori-preservation of statistical power. Single dosing did not appear to induce PSA declines.[7] Another trial (BC1-04) of 122 patients who received 3 doses of either 25, 50, or 80 kBq/kg q 6 weeks (corresponding to 28, 55 and 88kBq/kg after implementation of the NIST update) did find that the lower dose group had fewer PSA responders and alkaline phosphatase responder.[8]

Collectively, this data led to double-blind, randomized, multiple dose, phase III multicenter trial of Radium-223 50kBq/kg administered every 4 weeks for 6 doses compared to placebo in mCRPC (ALSYMPCA). The primary endpoint of this trial was overall survival, and a 2.8 mo survival advantage or 31% reduction in the risk of death was demonstrated.[4] The results of both the interim and updated analysis, revealed that OS was significantly longer in patients treated with Radium-223 plus best standard of care compared to patients treated with placebo plus best standard of care.

The ALYMPCA trial however did not address the effect of pain palliation in a rigorous manner or one in which this agent could be used for a pain label. Radiographic imaging was also not systematically addressed. These are two of the most compelling unanswered questions about this agent that can be addressed in the current trial.

Initial prospective data about pain response is available from a prior phase 2, double-blind, randomized, multinational study that evaluated the pain relief of a single injection of Radium-223 at dose concentrations of 5, 25, 50, or 100 kBq/kg corresponding to 6, 28, 55 or 110 kBq/kg after implementation of the NIST update) for CRPC patients with painful bone metastasis.[7] The primary endpoint was to measure the pain-relieving effect of a single dose of Radium-223 based on pain index composed of visual analogue scale (VAS) and analgesic use. The secondary endpoints included: change in BPI pain severity index (worst, least and average pain and pain experienced at current time) from baseline; BPI functional interference index (general activity, mood, walking ability, and work, relations with other people, sleep and enjoyment of life) and pain relief from medication; duration of pain relief, OS and safety.[7]

Patients (n=100) with progressive CRPC with testosterone levels <50 ng/dL after orchiectomy or on androgen ablation therapy who have bone pain ≥2 on the BPI were assigned to 1 of 4 single-dose groups of 5 kBq/kg (corresponding to 6kBq/kg after implementation of the NIST) (n=26), 25 kBq/kg (corresponding to 28kBq/kg after implementation of the NIST) (n=25), 50 kBq/kg (corresponding to 55kBq/kg after implementation of the NIST) (n=25), or 100 kBq/kg (corresponding to 110kBq/kg after implementation of the NIST) (n=24) of Radium 223 administered IV.[7] Follow-up visits were conducted at 2, 4, 8, 12, and 16 weeks post-injection to access the palliative response. At Week 8, patients with no palliative response could be withdrawn from the study. Additionally, patients were evaluated annually for up to 2 years after dosing for long-term safety and survival.

A statistically significant dose response occurred at Week 2 (*P*=0.035 [Jonckheere-Terpstra test]).[6] At Week 8 there were 40%, 63%, 56%, and 71% pain responders (pain index ≤4) in the 5, 25, 50, and 100 kBq/kg groups (corresponding to 6,28,55 and 110kBq groups after implementation of the NIST) , respectively. Of the responders, 6/20 (30%), 8/19 (42%), 8/18 (44%), and 11/21 (52%) reached complete (pain index 1) or marked pain response (pain index 2), respectively.

At Week 8, the mean daily diary pain decreased by 30 mm average in the responder group, remained unchanged in the stable group, and decreased 12 mm in the pain progression group.[7] The pain progression group was allowed to increase analgesics. Up to week 8, fewer patients in the higher dose groups (50 and 100 kBq/kg) (corresponding to 55 and 110 kBQ/Kg after implementation of the NIST) required in increases in analgesia compared to lower dose groups.

Mean pain relief duration of 44 days for higher-dose (50 and 100 kBq/kg) corresponding to 55 and 110 kBQ/kg after implementation of the NIST) groups, 28 days for 5 kBq/kg (corresponding to 6kBq/kg after implementation of the NIST, and 35 days for 25 kBq/kg (corresponding to 28kBq/kg after implementation of the NIST) dose groups.[7] There was not a significant dose-response for pain relief duration.

BPI data showed significant dose-dependent treatment effect at the 8-week point (*P*=0.040 [Jonckheere-Terpstra test]).[7] For patients with a pain response, there was a significant decrease in BPI pain severity for all 4 dose groups (*P*=0.05, *P*=0.001, *P*=0.002, and *P*=0.0006 [Wilcoxon signed rank test]).

Post-hoc analysis showed a significant dose-response among pain responders in mean daily pain at Week 8 (*P*=0.008, *P*=0.0005, *P*=0.002, and *P*<0.0001).[7] Improved BPI functional interference index was also found for pain responders across all doses (*P*=0.04, *P*=0.01, *P*=0.002, and *P*=0.02 [Wilcoxon signed rank test]).

AEs were reported for 97% of all participants, with approximately half reporting at least 1 serious AE.[7] No trends were found with the increase of dose in the number, nature, or seriousness of AEs. Differences in AEs were not found across treatment groups. Disease progression was the most frequent AE with an outcome of death. Non-hematological AEs most frequently reported across all groups were nausea, fatigue, vomiting, diarrhea, bone pain, urinary tract infection, and peripheral edema.

The most common hematological AEs reported were anemia (11%) and hemoglobin decrease (15%), but neither was dose dependent.

Clinical safety summary

The pharmacokinetics, biodistribution, and dosimetry in humans have been established (Appendix D). When intravenously administered, this agent is eliminated from blood quickly and taken up by bone. It is excreted via the gastrointestinal tract with minimal exposure to the kidneys and bladder (less than 1-5% at 48 hours).

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. In the ALSYMPCA randomized trial, 2% of patients in the Xofigo arm experienced bone marrow failure or ongoing pancytopenia, compared to no patients treated with placebo. There were two deaths due to bone marrow failure. For 7 of 13 patients treated with Xofigo bone marrow failure was ongoing at the time of death.

Table 1 Adverse Reactions in the Phase III Randomized Trial shows adverse reactions occurring in ≥ 1% of patients and for which the rate for Ra-223 dichloride exceeds the rate for placebo.

Table 1 Adverse Reactions in the Phase III Randomized Trial[4]

System/Organ Class Preferred Term	**Radium-223 (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
Anemia	31	13	31	13
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 were 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 treated patients and at a higher incidence than in placebo-treated patients was lymphopenia (0.8% vs. 0.3%).

1.3 Rationale

1.3.1 Rationale for conducting the study

The prevalence of baseline bone pain in contemporary trials of patients with metastatic castration-resistant prostate cancer is estimated between 2-45%. Despite the prevalence of bone pain, contemporary clinical trials have not addressed an agent's ability to palliate pain in a fashion that could be used for regulatory approval for this indication. The last agent to establish pain relief was in 1996 with mitoxantrone/prednisone.[9] Other agents, such as Strontium-89 and Samarium-153 EDTMP, are approved to palliate painful bone metastases. However, both agents are beta-emitting bone seeking radiopharmaceuticals and therefore have been limited for concern of bone marrow toxicity. The phase II trial would label Radium-223 FDA approved for use in palliating pain with minimum damage to surrounding bone and substantially less marrow toxicity, allowing better quality of life.

Anticipated *benefits* of the treatment include the following:

-Palliation of bone pain with associated improvement in QOL

- Prolongation of overall survival, most definitively demonstrated in the randomized phase II trial

-Anti-tumor efficacy as measured by chemical parameters of bone turnover

- Minimal toxicity

Anticipated risks attributed to Ra-223:

- AEs: Gastrointestinal events (transient diarrhea, nausea and vomiting)

- Transient reduction in neutrophil count. Mild to moderate reversible myelosuppression may occur.

- Ra-223 is a radioactive drug, and may, in the longer term (over several years), induce other primary cancers and bone marrow changes. From the data derived so far up to 2 years, there are no reports of long term toxicity.

The risk profile attributed to Ra-223 is favorable compared with available products in prostate cancer.

1.3.2 Rationale for dosage selection

The dose selected for this agent is (50 kBq (0.00135 mCi) (55kBq (.0015 after NIST update) administered every 4 weeks for 6 doses. This was selected based on prior studies, including the dose used in the randomized; phase III study that demonstrated a 31% reduction in the risk of death in comparison to placebo. This is the FDA-approved dose.

1.3.3 Rationale for correlative studies

A. Imaging

Routine imaging studies were not mandated by the ALSYMPCA trial. It is therefore not known what impact, if any, treatment with Radium-223 has on standard imaging studies, or the nature of the relationship between changes in standard imaging studies and cancer outcomes. Post-treatment changes on standard bone scintigraphy and cross sectional imaging will be systematically examined in this study, using PCWG2 criteria. [1]

Unfortunately, bone scintigraphy does not demonstrate direct changes in metastatic disease, but rather on the surrounding bone. FDG has the capacity to demonstrate post-treatment changes in underlying tumor, even in bone, for patients with CRPC.[10]

Recently, CMS has reviewed the evidence of using FDG as a post-treatment indicator of treatment effects in CRPC, concluded that it has utility as a post-treatment indicator of treatment effects, and that use of FDG PET results in significant changes in management. Based on studies at MSKCC, CMS found that "FDG PET CT could be valuable even for assessing activity of bone metastases of prostate cancers in a large majority of patients".[11,12]

Consequently, CMS proposed that use of FDG PET/CT when used to guide subsequent anti-tumor treatment strategy for patients with cancer of the prostate is reasonable and necessary under § 1862(a)(1)(A).[12]

Little is known about the anti-tumor effects of Ra- 223 in prostate cancer in regards to glucose metabolism evaluated by FDG PET/CT. However, twenty patients with metastatic breast cancer receiving Ra-223 were recently evaluated by FDG PET. Analysis revealed that a third of the target lesions defined as the standard uptake value (SUV_{max})>twice normal liver uptake and a diameter >15mm on PET CT showed a significant metabolic decrease ($\geq$25% reduction in SUV_{max} from baseline or complete disappearance of lesions) after 2 treatment doses. [13] FDG PET/CT will

be performed on patients in centers where such imaging is feasible, and in patients who consent to such additional imaging.

B. Serum Biomarkers

The primary serum biomarker that appears to be altered with Radium-223 are markers of bone turnover, more so than PSA. In study BC1-02 (33 patients received 4 doses of 50 kBq (0.00135 mCi) corresponding to (55kBq (.0015 after NIST update) . at 4 week intervals, 31 patients received placebo), results showed a significant decline in serum bone markers i.e. bone-ALP (the study primary efficacy endpoint), PSA response and a delayed time to PSA progression. Overall survival was prolonged in the Ra-223 group, with an increase in median survival time from 46 to 65 weeks (full analysis set). At 2 years, 10 of 33 of patients (30%) treated with Ra-223 were alive compared to 4 of 31 of placebo patients (13%). The results obtained with the biochemical markers for bone-turnover (bone-ALP, CTX-1, Procollagen Type I N-Propeptide (PINP)) and tumour load (PSA) support the presence of a treatment effect during the treatment period and for one to two months after the end of treatment. These data suggest that increasing treatment to six injections at 4 week intervals may further delay disease progression. A beneficial trend in the survival data supported a treatment effect, although survival data in 64 patients should be interpreted with caution.[6] However, the ALSYMPCA trail which was a randomized phase III placebo controlled trial did show a survival advantage or 31% reduction in the risk of death with Radium-223.

C. Tiredness and Pain Interference

Tiredness will be measured via the worst fatigue item (item #3) of the Brief Fatigue Inventory (BFI), which asks patients to "Please rate your fatigue (weariness, tiredness) by indicating the one number that best describes your WORST level of fatigue during the past 24 hours," with rating via an 11-point numerical rating scale anchored by zero demarking "No fatigue" and 10 demarking fatigue "As bad as you can imagine." The BFI is a well-established and validated tool that has been used in myriad prior cancer trials.[14] (See Appendix E for a copy of the Brief Fatigue Inventory, item #3)

Interference with general activity and sleep related to pain will be assessed by the item from the Brief Pain Inventory that asks patients to "Circle the one number that describes how pain has interfered with your general activity (or sleep) " using an 11-point numerical rating scale anchored by zero demarking "Does not interfere" and 10 demarking "Interferes completely" (Appendix F). This item demonstrates strong psychometric properties in prior research.[15]

2. OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to determine the effects of pain palliation with Radium-223.

2.2 Secondary Objectives

2.2.1 To assess the impact of treatment on markers of bone turnover

2.2.2 To assess the impact of treatment on PSA
2.2.3 To assess the impact of treatment on time to radiographic progression
2.2.4 To assess the impact of treatment on quantifiable imaging biomarkers assessing bone metabolism
2.2.5 To assess the impact of treatment on tiredness
2.2.6 To assess the toxicity of treatment
2.2.7 To assess the impact of treatment on pain interference specifically evaluating its affect on general activity and sleep as measured by the BPI
2.2.8 To assess the impact of treatment on time to pain progression
2.2.9 To assess the impact of treatment on change in analgesic use

3. PATIENT SELECTION

3.1 Target Population

Men with symptomatic metastatic castration-resistant prostate cancer.

3.2 Inclusion Criteria

To be included in this study, patients should meet all of the following criteria:

- Males aged 18 years of age and above
- Histological or cytological proof of prostate adenocarcinoma
- Castrate serum testosterone level: ≤50 ng/dL (≤1.7 nmol/L)
- Patients, who have experienced disease progression despite initial hormonal therapy, either by orchiectomy or by using a GnRH agonist in combination with an anti-androgen, must first progress through anti- androgen withdrawal prior to being eligible. The minimum timeframe to document failure of anti-androgen withdrawal will be four weeks. Patients on second-line (or beyond) hormonal maneuvers, and patients who had no PSA decline on combined androgen blockade as first line therapy, need not progress through AAW in order to be eligible.
- Known progressive castration-resistant disease, defined as:
    - Serum PSA progression defined as two consecutive increases in PSA over a previous reference value within 6 months of first treatment, each measurement at least one week apart. Serum PSA at screening ≥ 2 ng/mL

      or

    - Documented appearance of new lesions by bone scintigraphy
- ECOG Performance Status of 0-2 (Appendix A: Performance Status Criteria)
- 2 or more bone metastases demonstrated on bone scintigraphy
- Pain at baseline as measured by a BPI worst pain score average of ≥ 3. The BPI worst pain score average will be based on the worst pain scores completed by the patient in the 7 consecutive pretreatment days. A minimum of 4 days of pain scores must be completed by the patient in the 7 day window in order to calculate the average worst pain score. The investigator will optimize the subject's pain regimen prior to study entry.

- Normal organ function with acceptable initial laboratory values:
  - WBC $\geq 3 \times 10^9$ /L
  - ANC $\geq 1.5 \times 10^9$ /L
  - Platelets $\geq 100 \times 10^9$ /L
  - Hemoglobin $\geq$ 9.0 g/dL
  - Creatinine < 1.5 x institutional upper limit of normal (ULN)
  - Bilirubin ≤ 1.5 x ULN
  - AST/ALT ≤ 2.5 x ULN
  - Albumin > 25 g/L
- All acute toxicities as a result of any prior treatment must have resolved to NCI-CTCAE v4.0 Grade 1 or less at the time of signing the Informed Consent Form (ICF) [**Note:** Ongoing grade 2 neuropathy as a result of treatment with a cytotoxic chemotherapy regimen is permitted]
- Life expectancy of at least 6 months
- Willing and able to provide written informed consent and HIPAA authorization for the release of personal health information

  NOTE: HIPAA authorization may be either included in the informed consent or obtained separately
- Willing and able to comply with the protocol, including follow-up visits, examinations as well as having the ability to self-report pain and fatigue using a PRO instrument
- Willingness to use adequate methods of contraception beginning at the signing of the ICF until at least 30 days after the last dose of study drug

3.3 Exclusion Criteria

Patients that meet any of the criteria listed below will not be eligible for study entry:

- Prior exposure to Radium-223
- Received an investigational therapy within the 4 weeks prior to registration, or is scheduled to receive one during the treatment period
- Received a new anti-cancer agent within 4 weeks prior to registration
- Received external beam radiotherapy within 4 weeks prior to registration
- Received systemic therapy with radionuclides (e.g. strontium-89, samarium-153, rhenium-186 or rhenium-188) for the treatment of bone metastases
- Treatment with cytotoxic chemotherapy within 4 weeks prior to registration
- Symptomatic nodal disease, i.e. scrotal, penile or leg edema.
- Visceral metastases (including cerebral metastases) from CRPC (>2 lung and/or liver metastases [size ≥2cm]; Lymphadenopathy exceeding 6 cm in short-axis diameter or any

size pelvic lymphadenopathy if it is thought to be a contributor to concurrent hydronephrosis), as assessed by CT, MRI or chest X-ray within the 8 weeks prior to registration

- Concurrent chemotherapy. Patients may be on other non-chemotherapy anti-cancer treatments, per FDA labeling of Radium-223, provided that these are not changed during the primary pain assessment period
- Major surgery within 30 days prior to registration
- Imminent spinal cord compression based on clinical findings and/or magnetic resonance imaging (MRI). Treatment should be completed for spinal cord compression.
- Patients with a, "currently active," second malignancy other than non-melanoma skin cancers or non-invasive bladder cancers or other in-situ or non-invasive malignancies. Patients who have completed therapy for a prior malignancy and are free of disease for ≥3 years are eligible.
- 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 4.0 Grade 2
    - Cardiac failure New York Heart Association (NYHA) III or IV
    - Crohn's disease or ulcerative colitis
    - Bone marrow dysplasia
    - Fecal incontinence
- Any other condition which, in the opinion of the Investigator, would make the subject unsuitable for trial participation

4. PATIENT REGISTRATION AND ENROLLMENT PLAN

4.1 Enrollment Plan

4.1.1 Participating Study Centers

This study is anticipated to be conducted at 3 sites.

4.1.2 Recruitment

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at participating centers from Medical Oncology, Radiation Oncology and Urology offices. Investigators will screen the patient's medical records for suitable research study subjects and discuss the study and their potential for enrolling in the research study.

4.2 Registration Procedure

After eligibility screening and confirmation that a patient is eligible, patients who are selected to participate will be registered with the PCCTC Caisis EDC, the PCCTC Clinical Data Management System (CDMS). A record of patients who fail to meet eligibility criteria (i.e., screen failures) will be maintained. Patient registration must be complete before beginning

any treatment or study activities. A complete, signed study consent and HIPAA authorization are required for registration.

4.2.1 PCCTC Registration:

Confirm eligibility as defined in Section 3 Patient Selection.

Obtain informed consent, by following procedures in Section 11.4 Written Informed Consent

Obtain completed or partially completed protocol specific Eligibility Checklist.

All participants will be registered through PCCTC Caisis EDC, the PCCTC's CDMS.

To complete registration and enroll a participant, the study staff at that site must contact the designated research staff at PCCTC to notify him/her of the participant registration. The site staff then needs to email registration/eligibility checklist and source documents to the PCCTC at PCCTC@mskcc.org. (Note: Source documentation of eligibility is not required for MSKCC participants.)

These documents must be sent for each enrollment within 24 hours of the informed consent form being signed.

Upon receipt, the research staff at PCCTC will conduct an interim review of all documents for all non-MSKCC participants. If the eligibility checklist or source documentation is missing, the patient will be registered pending enrollment and the site is responsible for sending the completed registration documents within 30 days of the consent.

If the external registration submission is complete, the participating site IRB has granted approval for the protocol, and the site has been activated by MSKCC, PCCTC will register the non-MSKCC participants. MSKCC participants will be fully registered by MSKCC.

Once the participant is registered, the participant will be assigned a PCCTC Caisis Subject ID. This number is unique to the participant and must be written on all data and correspondence for the participant. This PCCTC Caisis Subject ID will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

4.2.2 Institutional Registration

Patient registration at each study site/institution will be conducted according to the institution's established policies. Patients must be registered with PCCTC, MSK and their local site/institution before beginning any treatment or study activities.

At MSKCC, all participants must be pended with MSKCC's Protocol Participant Registration (PPR) Office prior to submitting registrations to PCCTC.

PCCTC will register all non-MSKCC participants with MSKCC's Protocol Participant Registration Office (PPR) per MSKCC's guidelines.

MSKCC will register all MSKCC participants with MSKCC's Protocol Participant Registration Office (PPR) per MSKCC's guidelines.

5. TREATMENT/INTERVENTION PLAN

The following assessments and procedures will occur during the study. A schedule of assessments is shown below.

	Screening Period		**Treatment Period**												**Follow up visit** (visits occur every 3 months +/- 1 week)[e,g]
	Week -4[a]		Wk1 (within 5 days after the run-in period ends)	Wk4	Wk5	Wk8	Wk9	Wk12	Wk13	Wk16	Wk 17	Wk20	Wk21	Wk24	Wk25/ Safety FU	
		Run-in Period														
Ra-223			X		X		X		X		X		X			
Informed consent	X															
Eligibility criteria/ Demographics / Medical history	X															
Testosterone level	X															
Imaging assessments[b]	X								X						X	X
Physical exam	X		X		X		X		X		X		X		X	X
Vital signs	X		X		X		X		X		X		X		X	X
Performance status	X		X		X		X		X		X		X		X	X
Clinician reported			**X----------X**													

adverse events															
Concomitant meds	X		**X----------X**												
ECG	X		**As clinically indicated**												
Pain scale (BPI Short Form using a PRO instrument x7days)		X[f]		X		X		X		X		X		X		X
Fatigue scale (BFI item using a PRO instrument x7days)		X		X		X		X		X		X		X		X
Analgesic diary[h]		X		X		X		X		X		X		X		X
Hematology[c]	X		X		X		X		X		X		X		X	X
Serum biochemistry[d]	X		X		X		X		X		X		X		X	X
PSA	X		X		X		X		X		X		X		X	X
Bone markers	X						X		X							

Abbreviations: BFI=Brief Fatigue Inventory; BPI=Brief Pain Inventory; CT=computerized tomography; ECG=electrocardiogram; MRI=magnetic resonance imaging; PSA=prostate-specific antigen.

[a] Informed consent must be obtained, and radiologic assessments will be obtained within 4 weeks of study start date.

[b] Imaging assessments will be performed every 12 weeks ± 1 week. Bone scan, FDG PET (FDG will be done in consenting patients and is considered optional) , CT scan or MRI of the abdomen and pelvis and CT scan of the chest or Chest X-ray

[c] Hematology: White blood cells count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), platelet count (UNVPLT), neutrophils (NEUTP), lymphocytes (LYMP), monocytes (MONP), eosinophils (EOSP), basophils (BASOP)

[d] Serum biochemistry: calcium (CA), albumin (ALB), total protein (TP), sodium (NA), potassium (K), chloride (CL), blood urea nitrogen (BUN), creatinine (CREAT), alkaline phosphatase (ALK), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBILI), lactate

dehydrogenase (LDH), gamma-glutamyl transpeptidase (GGT), phosphate (PHOS), magnesium (MG), glucose (GLU), carbon dioxide (CO2)

[e] Subjects should be followed up every 3 months following the safetly follow-up visit for a total of 2 visits or until initation of another therapy and be assessed for any potential long term toxicity as well as key efficacy parameters

[f] Subjects will indicate their daily pain score for 7 days during the 28 day screening period to establish that their average baseline pain score is ≥3 as measued for 4 of 7 days.

[g] During the follow-up period, subjects will answer questions on the BPI and BFI as well as enter information on their analgesic dairy for at least 4 of 7 days prior to their scheduled follow up visit

[h] Subjects will update their analgesic dairy daily during the run-in period and daily during the pain assessment periods throughout the trial

5.1 Screening/Pretreatment Assessment (Day -28 to Day -1)

Before initiating any screening activities, the scope of the study should be explained to each patient. Patients should be advised of any known risks inherent in the planned procedures, any alternative treatment options, their right to withdraw from the study at any time for any reason, and their right to privacy. After this explanation, patients should be asked to sign and date a research authorization/HIPAA form and an IRB-approved statement of informed consent that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50.

The screening visit will determine patient eligibility according to the inclusion and exclusion criteria. The following assessments will be performed at this visit:

- Obtain informed consent and research authorization
- Record demographics (including age) and medical history (including prior treatment for prostate carcinoma)
- Physical exam
- ECOG performance status
- Vital signs [body temperature, blood pressure, pulse, respiratory rate, weight, height]
- Obtain histologic and radiologic confirmation of disease
- Confirm eligibility according to the inclusion/exclusion criteria
- Perform laboratory tests [hematology, serum biochemistry, PSA, testosterone level, bone markers]
- ECG
- Baseline imaging assessments: Bone scan, FDG PET (in consenting patients at centers that agree to perform FDG PET scans), CT scan or MRI of the abdomen and pelvis and CT scan of the chest or Chest X-ray]

Relevant information should be documented. The institutional registration should be finalized, and appropriate documents (i.e., signed informed consent, research authorization/HIPAA form, and supporting source documentation for eligibility questions) emailed to the lead site/sponsor.

Information for patients who do not meet the eligibility criteria to participate in this study (i.e., screening failures) should be captured in consortium database at the pretreatment assessment.

*5.1.1 **Run-In Period (Day -7 to Day -1 +/- 5 days)***

During the Run-In Period, subjects will self-report pain and fatigue using a PRO instrument daily for 7 days and record analgesic medication information on a paper pain medication diary to establish that their BPI average baseline pain score is $\geq$3 as measured for a minimum of 4 of the 7 days (See Appendix I for instructions). This data will be used to confirm eligibility based on pain experience. Upon confirmation of eligibility, the subject's registration will be completed and the subject must start treatment within 5 days of registration.

If run-in requirements are not met with respect to pain score, subjects may be eligible to rescreen at a later time.

5.2 Treatment/Intervention Period (Week 1, Day 1 to Week 25, Day 169 (treatment visits have a window of ±3days))

Unless otherwise specified, all visit procedures are to be performed prior to Radium-223 administration on the day of the visit. Radium -223 will be administered every 4 weeks for 6 doses at a dose of (50 kBq (0.00135 mCi) (55kBq (.0015 after NIST update) Because ALSYMPCAa did not assess radiographic assessments during treatment, neither radiographic progression nor PSA progression should be used to discontinue treatment. However, patients are *permitted, per FDA labeling,* to be maintained on other anti-cancer therapies in addition to Radium-223 provided that these are not changed in the midst of pain assessments. Other-cancer therapies must be initiated 4 weeks prior to the run-in period. Patients with an increase in pain of 2 points on their BPI worst pain item compared to baseline and confirmed at least 2 weeks later will be considered to be treatment failures and will be taken off trial. In the absence of clinical progression, patients will continue to receive all six treatments, and will continue treatment until clinical progression, unacceptable toxicity, or any criteria in Section 5.6 Removing Patients from the Protocol. Patients will return to the clinic every 4 weeks for the following assessments:

- Physical exam
- ECOG performance status
- Vital signs [body temperature, blood pressure, pulse, respiratory rate, weight]
- ECG (as clinically indicated – not required at every visit)
- Lab tests [hematology, serum biochemistry, PSA, bone markers (to be done at the Wk 9 and Wk 13 visit)]
- Clinician reported adverse events and concomitant medications will be monitored continuously throughout the study
- Imaging assessments will be performed every 12 weeks ± 1 week during treatment period (Week 13, Week 25 [Safety Follow-Up Visit]): Bone scan, FDG PET (in consenting patients at participating centers), CT scan or MRI of the abdomen and pelvis and CT scan of the chest or Chest X-ray]
- During the treatment period, as outlined in the table above, subjects will self-report information on pain, fatigue and health-related quality of life via a PRO instrument (See Appendix I for instructions). Data will be entered by the subject daily during the 7 day reporting period according to the scheduled outline in the above table. Subjects will also update their analgesic dairy during this 7 day period as well. All PRO entries should be done at home prior to visits to the clinic for either regularly scheduled visits or imaging appointments. If for any reason PRO entries are done while the subject is at the clinic, the staff should not provide any input or assistance other than technical help on using the system.

5.2.1 Safety Follow-Up Visit (Week 25±7 days)

Once a patient has completed treatment with 6 doses of Radium-223, or the patient is prematurely discontinued from treatment for any reason specified in Section 5.6 Removing Patients from the Protocol, the patient will complete a safety follow-up visit including the following assessments:

- Physical exam
- ECOG performance status
- Vital signs [body temperature, blood pressure, pulse, respiratory rate, weight]
- ECG (as clinically indicated – not required at every visit)
- Pain scale (BPI Short Form using a PRO instrument)
- Fatigue scale (BFI item using a PRO instrument)
- Analgesic diary
- Lab tests [hematology, serum biochemistry, PSA]
- Adverse events and concomitant medications will be monitored continuously throughout the study

For the pain and fatigue scale, data will be entered by the subject daily during the 7 day reporting period prior to their safety visit. Subjects will also update their analgesic dairy during this 7 day period as well.

5.3 Follow-Up

- Patients will be evaluated every 3 months (+/- 1 week) until 6 months after the safety follow-up visit for a total of 2 visits or until initation of another therapy. The following assessments will be performed at these visits:
- ECOG Performance Status
- Pain scale (BPI Short Form using a PRO instrument)
- Fatigue scale (BFI item using a PRO instrument)
- Analgesic diary
- Lab tests [hematology, serum biochemistry, PSA]
- Imaging Assessments: Bone scan, FDG PET (FDG will be done in consenting patients and is considered optional) , CT scan or MRI of the abdomen and pelvis and CT scan of the chest or Chest X-ray

The follow-up visit should be calculated from the date of the safety follow-up visit for Radium-223. For the pain and fatigue scale, data will be entered by the subject daily during the 7 day reporting period prior to their follow-up visit. Subjects will also update their analgesic dairy during this 7 day period as well.

5.4 Clinical and laboratory assessments

Medical History

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication
- Start before signing of the informed consent
- Considered relevant to the study

ECOG Performance Status

Performance status will be assessed using ECOG performance status criteria. See Appendix A: Performance Status Criteria for a KPS-ECOG conversion chart.

Vital Signs

Vital signs include body temperature, blood pressure, respiratory rate, pulse, weight and height. Height will be performed at screening only.

Physical Exam

The physical exam will include a full review of the body systems.

Electrocardiogram (ECG)

A 12-lead ECG will be recorded at screening and whenever an Investigator determines it clinically indicated throughout the treatment period.

Adverse Event Monitoring

Patients will be closely monitored throughout the study for adverse events, at least every four weeks. Adverse events and other symptoms will be graded according to NCI CTCAE v4.0. Adverse events will be monitored from the first dose of *Radium-223* through *4* weeks following the last administration or until all study drug-related toxicities resolve, stabilize, return to baseline or are deemed irreversible, whichever is longer.

Laboratory Test Assessments

Hematology: white blood cells count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), , platelet count (UNVPLT), neutrophils (NEUTP), lymphocytes (LYMP), Serum Biochemistry: calcium (CA), albumin (ALB), total protein (TP), sodium (NA), potassium (K), chloride (CL), blood urea nitrogen (BUN), creatinine (CREAT), alkaline phosphatase (ALK), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBILI), lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase (GGT), phosphate (PHOS), magnesium (MG), glucose (GLU), carbon dioxide (CO2)

Serum PSA (PSA)

Bone markers: bone specific alkaline phosphatase (BAP), serum N-telopeptide (SNTX), serum C-telopeptide (SCTX), procollagen type I N-terminal propeptide (PINP)

Testosterone level *(TEST)*

BPI short form (pain scale)

A Patient Reported Outcome (PRO) instrument will be performed by patients to assess level of pain which includes a change in BPI worst pain item from baseline (See Appendix I for instructions). BPI functional interference index (general activity, sleep) will be collected.

Measure of fatigue

Patient Reported Outcome (PRO) instrument will be performed by patients to assess fatigue using the Brief Fatigue Inventory (BFI). Patients will be asked to "Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours," with rating via an 11-point numerical rating scale anchored by zero demarking "No fatigue" and 10 demarking fatigue "As bad as you can imagine."

Analgesic diary

Records daily intake of analgesic medications. A question confirming that subject's pain medication diary has been completed is included in the PRO instrument.

Tumor Assessment and Bone Scan

Radiographic disease assessment will be obtained every 12 weeks during active treatment and every 3 months during the long-term follow-up portion using PCWG2 criteria as described in Section 8.3 Therapeutic Response.

5.5 Dosing Delays and Dose Modifications for Toxicities

At each study visit for the duration of their participation in the study, patients will be evaluated for adverse events (all grades), serious adverse events (SAEs), and adverse events that require study drug interruption or discontinuation. Patients discontinued from the treatment phase of the study for any reason will be followed for toxicity until approximately 4 weeks after the last dose of the study drug or until all study drug-related toxicities resolve, stabilize, return to baseline or are deemed irreversible, whichever is longer.

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 may be on other non-chemotherapy anti-cancer treatments, per FDA labeling of Radium-223, provided that these are not changed during the period of pain assessments.

Patients with a rising PSA should not be considered to have progressive disease, as a rising PSA does not imply lack of clinical benefit with treatment radium-223.

Patients with radiographic progression are not required to discontinue treatment or to be defined for this trial as having disease progression, as there are no known data associating such radiographic findings with a lack of clinical benefit with radium 223.

Patients with unequivocal clinical progression should be considered treatment failures, and treatment under the auspices of the protocol will be discontinued.

Myelosuppression

If a patient experiences Common Terminology Criteria for Adverse Events[1] (CTCAE)grade 3-4 neutropenia or thrombocytopenia lasting > 14 days, further study drug administrations must be discontinued.

If a patient experiences CTCAE grade 3-4 neutropenia the study drug administration should be delayed until recovery to grade 2 (minimum 1.0×10^9 /L) or better.

In case of thrombocytopenia grade 3-4 the study drug administration should be delayed until recovery to CTCAE grade 2 (minimum 50×10^9 /L) or better.

In case of hemoglobin CTCAE grade 3-4, the value needs to recover to CTCAE grade 2 (minimum 8.0 g/dL) or better before next study drug administration. Blood transfusion is acceptable between study drug administrations.

Gastrointestinal events:

Diarrhea:

No prophylactic treatment for diarrhea is recommended. Antidiarrheals can be used when needed. A further dose of study medication should not be given before recovered to CTCAE grade 2 or baseline.

Nausea/Vomiting:

No prophylactic treatments for nausea or vomiting are recommended, but anti-emetic drugs can be used when needed. A further dose of study medication should not be given before recovered to CTCAE grade 2 or baseline.

Constipation:

Patients can continue laxative as concomitant medication, but start of prophylactic treatments before study drug injection are not recommended. Laxative can be used when needed. A further dose of study medication should not be given before recovered to CTCAE grade 2 or baseline.

Spinal Cord Compression

[1] Common Terminology Criteria for Adverse Events, Version 4.0 (CTC AE); Published May 28, 2009

Patients, who experience spinal cord compression and require treatment with XRT in the treatment period prior to week 8, will be taken off-study and declared non-evaluable.

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.

Any Other Toxicity
If a patient experiences any non-hematological grade CTCAE grade 4 toxicity lasting > 7 days despite adequate treatment, further study drug administration must be discontinued.

5.6 Removing Patients from the Protocol

Patients will receive a maximum of 6 doses of Radium-223 on study unless one of the following criteria applies:

- Patient decides to withdraw from the study
- Symptomatic disease progression at any time
- Objective clinical disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) that may or may not be directly related to treatment but that, in the judgment of the treating physician, makes it dangerous for the patient to be retreated
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment, in the judgment of the investigator

Because an excessive rate of withdrawals can render the study uninterpretable, unnecessary withdrawal of patients should be avoided. When a patient discontinues treatment early, the investigator should make every effort to contact the patient and to perform a final evaluation. The reason(s) for withdrawal should be recorded.

5.6.1 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.

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

Patients who are withdrawn from the protocol per reasons stated above will be replaced, unless they are evaluable by criteria specified in Section 10.2.1 Analysis Populations.

5.7 Concomitant Medications

Because of the potential for drug-drug interaction, the concurrent use of all other drugs, over-the-counter medications, or alternative therapies taken within 2 weeks prior to the start of the study must be documented on the case report form (CRF).

Patients receiving bisphosphonates or denosumab (RANK-L inhibitor) may continue on these agents as standard practice throughout the study.

Patients who enter the trial receiving prednisone or steroids must continue on the same dose they were receiving at the time of baseline assessment.

Permitted

- Pain Regimen Modification Guidelines:
    - An attempt to optimize a pain regimen should be made prior to subject enrollment. The investigator will optimize the subject's pain regimen under advisement/guidance of the 2.2014 NCCN Adult Cancer Pain guidelines. Opioid rotation, use of adjuvants, institution of a sustained release medication to minimize frequent prn dosing will be utilized depending on the severity of pain, degree of opioid tolerance and side effects under advisement/guidance of the NCCN guidelines. Use and optimization of short acting opioids followed, if needed, by adding an extended-release or long-acting formulation described in the protocol reflect NCCN guidelines. The patient will usually be allowed rescue doses of short-acting opioids of 10% to 20% of 24-h oral dose (mg) as needed as per the NCCN guidelines.
    - At the time of enrolment, the subjects pain regimen will be graded according to the WHO analgesia ladder:

- Step 1- non-opioid analgesics
- Step 2- weak opioid (tramadol, codeine, hydrocodone)
- Step 3- strong opioid analgesic (morphine, oxycodone, fentanyl, oxymorphone, levorphanol, and methadone).
- NSAIDs, steroids and other adjuvant non-opioid analgesics can be included at each step of the analgesics ladder.

- 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).
- 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 other than chemotherapy for prostate cancer are permissible, provided that they are started before the patient's pain assessments, and are not changed during the pain assessments. These agents will be recorded in the CRFs. These treatments may include, but are not necessarily limited to: Luteinizing-Hormone-Releasing hormone (LHRH) analogs, surgery, flutamide, bicalutamide, nilutamide, estramustine, ketoconazole, corticosteroids, estrogens, abiraterone, and enzalutamide.

6. THERAPEUTIC AGENT

6.1 Description of Treatments

Radium -223 (will be supplied as ready to use vial solutions for intravenous administration. The dose will be (50 kBq (0.00135 mCi) (55kBq (.0015 after NIST update) administered every 4 weeks for 6 doses.

Ra-223 will be administered as slow bolus injection over 1 minute.

Written instructions for handling and administration of Ra-223 will be given.

Ra-223 injection is a ready-to-use, sterile, free from endotoxins, clear and colorless aqueous solution of Radium-223 dichloride ($^{223}RaCl_2$) for intravenous administration. The volume per vial is 6 mL, corresponding to 6.6 MBq after implementation of the NIST with a

radioactive concentration of 1,100 kBq/mL after implementation of the new NIST standard at the reference date. The product has a pre-calibration of 14 days.

Radium-223 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 1,100 kBq/mL after implementation of the NIST. The product has a pre-calibration of 14 days. When administered in a day other than the reference day, the volume should be corrected according to the physical decay table supplied with each shipment.

Radium Ra 223 dichloride is manufactured in Norway at a Bayer-contracted manufacturing site, IFE (Institute for Energy Technology), a specialized facility with a long history of manufacturing radiopharmaceuticals. The product is produced according to Good Manufacturing Practice (GMP).

Radium Ra 223 dichloride is then shipped to Cardinal Health for distribution in the United States. Cardinal Health prepares individualized patient ready doses based on patient weight and intended time of administration. The product is delivered in a glass vial, ready-to-use with a certified activity. Radium Ra 223 dichloride is shipped in a lead container with Type A radioactive packaging according to international transportation guidelines for radioactive materials. Patient ready doses to be utilized within study 14-098/c13-124 will be over-labeled with an "investigational use only" label at Cardinal prior to distribution to administering sites.

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.

6.2 Dosage Selected, Preparation, and Schedule of Administration

If the vials have been stored in a refrigerator, they should be left at room temperature for 1 hour prior to use. Ra-223 should not be diluted or mixed with any solutions.

The dose of Ra-223 is (50 kBq (0.00135 mCi) (55kBq (.0015 after NIST update) (unless, following discussions between the investigator(s) and sponsor, additional cohort(s) are added at intermediate Ra-223 dose levels between 25 and 55 kBq/kg). Radium Ra 223 dichloride will be administered as a bolus intravenous (IV) injection (up to 1 minute) at intervals of every 4 weeks for up to 6 cycles.

The dosage of Radium Ra 223 dichloride after implementation of the new 2015 NIST standard is 55kBq/kg body weight The patient dose is calculated based on date of injection, a decay correction (DK) factor specific to number of days from reference date applied to correct for physical decay of radium-223 , and patient weight. A table with DK values according to physical decay of the study medication will be provided with every shipment of Radium Ra 223 dichloride. Radium-223 is an alpha particle emitter with a physical $t^{1/2}$ of 11.4 days. After implementation of the NIST the radioactive concentration at the reference date is 1,100 kBq/mL

The volume to be administered for dosing is calculated as follows:

Volume to be = **Body weight (kg) × dose (55kBq/kg**

administered after implementation of the new NIST standard (mL)

b.w.)

DK factor × 1,100 kBq/mL

Filling of the syringe should take place in a fume cupboard or safety bench in the Radiopharmacy/Nuclear Medicine department. Personnel should wear medical gloves and eye protection during syringe filling to prevent contamination of the radioactive solution to skin and eyes. The individual responsible for study drug preparation will draw the correct volume of study drug into a syringe. Data regarding activity and volume to be injected for the various patients should be recorded on the study drug administration CRF page.

To maintain traceability, there is one syringe label set per injection, with three identical removable stickers with a unique serial number, in addition to information of the radioactive material. One sticker with the serial number should be attached to the drug preparation page, the other on the syringe and the third to the CRF study drug administration page.

The syringe should be handed over to the individual who will perform the administration. There is no need for shielding from alpha particle radiation during preparation and administration of the patient doses. Alpha particles from radioactive decay of Radium-223 and progeny are easily stopped by the thickness of a sheet of a paper or the walls of a glass vial.

Aseptic technique should be used in the administration of Ra-223. The investigational drug will be administered as a slow bolus intravenous injection. After administration, the equipment used in connection with the preparation and administration of Ra-223, is to be treated as radioactive waste and should be disposed of in accordance with hospital procedure for the handling of radioactive material. Written information about Ra-223 and instruction about handling and administration of radioactive material will be given to study personnel.

Treatment will be administered on an outpatient basis.

6.2.1 Supply, storage requirements, and special handling

A dedicated person, who has the responsibility delegated from the Principal Investigator, will have the overall responsibility for handling and storage of study drug at the centre; i.e., that the vials with study drug are correctly received and recorded, handled and stored safely and properly, and used in accordance with this protocol. A deputy person should also be nominated. The study drug is a radiopharmaceutical and should be handled by individuals who are qualified by training and experience in the safe handling of radiopharmaceuticals.

The Ra-223 vials must be stored inside their lead container (of approximately 4 mm thickness) in a secure facility. The study drug should be used within the designated expiration date by manufacturer. The radioactivity of Ra-223 is measured by use of a radioisotope dose calibrator, calibrated for the isotope Radium-223. The radioactivity in the vial will be controlled at the hospital as part of the drug accountability, upon receipt of Ra-223 and after dispensing. The radioactivity of the syringe will be controlled before and after administration.

6.2.2 Radiation protection

In general, the administration of radioactive drugs involves a potential risk for third persons due to radiation from the patient and possible contamination by spilt urine, feces, blood, etc. An advantage of using Radium-223 is that once injected, both alpha and beta particles are stopped by the patient's tissue. Some gamma radiation is emitted from Radium-223 and its daughters. However, due to the low activity injected and attenuation in the patient's body mass, the gamma radiation outside the patient's body is minimal, and therefore the product can be administered on an outpatient basis. The patient and his caretakers will receive instructions in accordance to regulatory requirements regarding hygiene precautions after receiving the radioactive drug, to minimize the risk of contamination. The exposure rate constants from patients receiving Ra-223 or from handling vials or syringes with Ra-223 have been measured and are felt to not be of clinical concern.

6.3 NIST Standardization

The quantification of radium-223 radioactivity in Xofigo (radium-223 dichloride; BAY 88-8223) is based on the primary standardization performed by the US NIST. National Institute of Standards and Technology prepares the standard reference material (SRM) using an official dial setting (primary standardization) as published.[16] The NIST SRM is used to calibrate the instruments in production and quality control for both the drug substance and drug product. Additionally, the NIST SRM is used to prepare the NIST traceable Ra-223 reference materials which are then sent to the end-users (e.g., nuclear medicine laboratory physicians or technicians) for dial-setting of their dose calibrators, to allow verification of the patient dose. In 2014, NIST performed a re-assessment of the primary standardization based on preliminary information suggesting a potential discrepancy of approximately 8-10% between the published NIST primary standardization[16] and results obtained by other national metrology institutes (United Kingdom, Germany, Japan). After completion of the re-assessment, NIST reported their findings[17] and had issued a revised NIST SRM in 2015. The discrepancy in the NIST standardization was determined to be −9.5% between activity values obtained using the old reference standard relative to the new primary standardization. Consequently the current numerical values need to be corrected by approx. + 10.5%.

The change in the numerical description of the patient's dose, product strength and labeled vial activity does not impact the safety or efficacy of Xofigo. The change in the NIST radium-223 standard has no impact on subjects; dose subjects are receiving, and will continue to receive.

Subjects will receive the same actual dose and volume that was studied in Study 15245 (BC1-06 dosimetry study) and is associated with the proven safety and efficacy of radium-223 dichloride, though the stated nominal radiation dose received has been updated to reflect the new standard.

7. ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a research patient during a clinical study or within 4 weeks post treatment, regardless of causality. This includes adverse clinical or laboratory findings, any adverse drug reaction (ADR), and an illness with onset during the study, or an exacerbation of preexisting illness or condition.

7.1.2 Serious Adverse Event (SAE)

The investigator must assess each event to determine if it meets the criteria for classification as an SAE or serious adverse drug reaction.

All SAEs that occur any time a patient is on study (i.e., as soon as the informed consent has been signed) or within 4 weeks of the last dose of Radium-223 must be recorded, regardless of the suspected relationship to the investigational agent. Any SAE occurring more than 4 weeks after the last dose of Radium-223 must be recorded if a causal relationship to the investigational agent is suspected.

An SAE/ADR as defined in the Code of Federal Regulations (21CFR312.32) is any event that:

- Results in death
- Is life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in congenital anomaly or birth defect
- Is medically significant in the opinion of the investigator

7.1.3 Progression of malignancy

Progression of a patient's malignancy should not be considered an AE, unless in the investigator's opinion, study treatment resulted in an exacerbation of the patient's condition. If disease progression results in death or hospitalization while on study or within 4 weeks of the last dose, progressive disease will be considered an SAE.

7.1.4 Life-threatening events

A life-threatening event is any AE that places the patient at immediate risk of death from the reaction as it occurs. It is not a reaction that, had it occurred in a more severe form, might have caused death.

7.1.5 Hospitalization or prolongation of hospitalization

Hospitalization encompasses any inpatient admission (even for less than 24 hours) resulting from a precipitating, treatment-emergent adverse event. For chronic or long-term patients, inpatient admission also includes transfer within the hospital to an acute or intensive care inpatient unit. Hospitalizations for administrative reasons or a non-worsening preexisting condition should not be considered AEs (e.g., admission for workup of a persistent pretreatment laboratory abnormality, yearly physical exam, protocol-specified admission, elective surgery). Preplanned treatments or surgical procedures should be noted in the baseline documentation. Hospitalization because of an unplanned event will be deemed an SAE.

Prolongation of hospitalization is any extension of an inpatient hospitalization beyond the stay anticipated or required for the original reason for admission.

7.1.6 Significant disability

Disability is a substantial disruption of the patient's ability to conduct normal life functions.

7.1.7 Congenital anomaly

If the female partner of a male patient becomes pregnant during the course of the study, the treating physician must be notified immediately. All confirmed pregnancies must be immediately reported to Bayer and PCCTC and recorded in PCCTC Caisis EDC. All pregnancies will be followed until resolution (i.e., voluntary or spontaneous termination or birth) and assessed for congenital anomalies and birth defects. Patients receiving Ra-223 will be instructed to avoid conception for at least 6 month after last administration of Ra-223.

7.1.8 Medical significance

An event that is not fatal or life-threatening and that does not necessitate hospitalization may be considered serious if, in the opinion of the investigator, it jeopardizes the patient's status and might lead to medical or surgical intervention to prevent any of the above outcomes. Such medically significant events could include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

The NCI CTCAE v4.0 handbook will be used for adverse event descriptions and grading.

Follow-up of adverse events should continue until the event and any sequelae resolve or stabilize at a level acceptable to the investigator and the study site/sponsor or medical monitor.

Events that are **not** considered serious adverse events include:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Elective or pre-planned treatment for a pre-existing condition that did not worsen
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Respite care

7.2 Recording and Grading

7.2.1 Recording

All observed or volunteered adverse events, regardless of treatment group, severity, suspected causal relationship, expectedness, or seriousness will be documented.

A clinically significant change in a physical examination finding or an abnormal test result (i.e., laboratory, x-ray, EKG) should be recorded as an AE, if it:

- Is associated with accompanying symptoms
- Requires additional diagnostic testing or medical or surgical intervention
- Leads to a change in study dosing or discontinuation from the study
- Requires additional concomitant drug treatment or other therapy, or
- Is considered clinically significant by the investigator

An abnormal test result that is subsequently determined to be in error does not require recording as an adverse event, even if it originally met one or more of the above criteria.

7.2.2 Grading severity

All adverse events will be graded based on NCI CTCAE version 4.0

7.2.3 Attributing causality

After grading for severity, the investigator must evaluate all clinical AEs and abnormal laboratory values for possible causal relationship to the investigational agent. Causality attribution will be decided using the criteria outlined in Table 6.

Table 6 Relationship of Adverse Event to Study Drug

Relationship	Description
Unrelated	AE is clearly not related to Ra-223
Unlikely	AE is doubtfully related to Ra-223
Possible	AE may be related to Ra-223
Probable	AE is likely related to Ra-223
Definite	AE is clearly related to Ra-223

Abnormal laboratory values of clinical significance that were present at baseline and did not change in severity or frequency during experimental therapy or intervention and those that can obviously be attributed to underlying disease will be recorded as unrelated and will not be considered when evaluating the maximum tolerated dose (MTD).

7.3 Reporting Adverse Events

7.3.1 Reporting serious adverse events

All SAEs, events determined to be medically significant by the treating Investigator, and unknown reactions or unexpected events should be reported lead site/sponsor and PCCTC within 24 hours of knowledge of the event using the contact information below. The initial report should include the following information at a minimum:

- Protocol # and title

- study identification number, sex, age at time of event
- Date the event occurred
- Description of the SAE
- Causal relationship to the study drug

The PCCTC SAE Report Form (Appendix B) will be used for reporting each SAE and should be submitted to the PCCTC within 3 calendar days of learning of the event. Severity, causality, action taken, concomitant medications, outcome, etc should be reported to the PCCTC as soon as possible.

Follow-up of adverse events should continue until the event and any sequela resolve or stabilize at a level acceptable to the investigator.

The PCCTC will facilitate all SAE reporting to the MSKCC IRB/PB within 5 calendar days of PCCTC awareness or identification of the event.

SAE contact information for the PCCTC, lead site/sponsor is listed below:

Lead Site Study PI
Michael Morris, MD
Memorial Sloan Kettering Cancer Center
Genitourinary Oncology Service
1275 York Avenue
New York, NY 10065
morrism@mskcc.org

PCCTC:
Prostate Cancer Clinical Trials Consortium
Phone: 646-888-0434/646-422-4383
Email: PCCTC@mskcc.org

7.3.2 Reporting SAEs to Bayer Pharmaceuticals, the drug supplier

All serious adverse events should be reported to Bayer within 24 hours of learning of the event. 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 of learning of the event.

Requirements for Reporting of Serious Adverse Events:
All SAEs must be reported to Bayer within 24 hours of the Principal Investigator's awareness and must include the following minimum information:

1.The name and contact information of the reporter
2. The name of the study drug(s)
3. A description of the reported SAE

4. A patient identified by one or more of the following:
    a. Patient initials
    b. Patient number
    c. Knowledge that a patient who experienced the adverse event exists
    d. Age
    e. Sex
5. An investigator assessment of study drug causality. For studies with combination therapy, a separate causality assessment should be provided for each study drug. Additional data which would aid the review and causality assessment of the case include but are not limited to:
    The date of onset
    The severity
    The time from administration of study drug(s) to start of the event
    The duration and outcome of the event
    Any possible etiology for the event
    The final diagnosis or syndrome, if known
    Action(s) taken, if any

Electronic Mailbox:	DrugSafety.GPV.US@bayer.com
Facsimile:	(973) 709-2185
Address: **Mail only:**	Global Pharmacovigilance - USA Bayer HealthCare P.O. Box 1000 Montville, NJ 07045-1000
Address: **FDX or UPS only**	340 Changebridge Road Pine Brook, NJ 07058

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

Phone:	1-888-842-2937

7.4 Safety Reports

PCCTC will distribute outside safety reports to the participating sites immediately upon receipt. Participating sites are responsible for submitting safety reports to their local IRB/PB as per their local IRB guidelines. All local IRB approvals/acknowledgments of safety reports must be sent to PCCTC upon receipt.

8. CRITERIA FOR OUTCOME ASSESSMENT/THERAPEUTIC RESPONSE

8.1 Primary endpoint

The primary endpoint of the study is a 30% decline in the BPI worst pain item from baseline to week 8, with a confirmed reduction at week 12 without an escalation of the subject's pain regimen from Step 1 to Step 2 or Step 2 to Step 3 of the WHO analgesic ladder.

The baseline BPI worst pain score average will be based on the worst pain scores completed by the patient in the 7 consecutive pretreatment days. A minimum of 4 days of pain scores must be completed by the patient in the 7 day window in order to calculate the average worst pain score.

8.2 Secondary endpoints

- Bone-ALP response will be described as:
  - Percentage of change from baseline to 12 weeks (or earlier for those who discontinue study therapy)
  - Maximum change (rise or fall) in bone-ALP during the treatment period reported for each patient as a waterfall plot
- Changes in total-ALP will be defined as for bone-ALP above
- PSA decline will be reported on all patients. Using PCWG2 guidelines [1], the percentage of change in PSA from baseline to 12 weeks, as well as the maximum decline in PSA will be reported for each patient using a waterfall plot.
- Progression, for those patients showing an initial decline in PSA from baseline, is defined as an increase in PSA that is ≥25% and ≥2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend).
- Progression, for those patients with no decline in PSA from baseline, is defined as an increase in PSA that is ≥25% and ≥2 ng/mL after 12 weeks. Note: PSA progression as such will not lead to study discontinuation
- Time to First Radiographic or Clinical Progression (TTFROCP) based on RECIST version 1.1 and Prostate Cancer Working Group 2 (PCWG2) definitions
- Changes in other bone markers:
  - Serum C-telopeptide (sCTX-1)
  - N-terminal propeptide of procollagen type 1 (PINP)
- Radiographic response through the RECIST criteria 1.1 will also be determined using FDG PET/CT to assess for treatment effect in bone.
- Time to pain progression, defined as time until a ≥2 point increase in pain compared to baseline confirmed at least 4 weeks later.
- Change in analgesic use assessed by the WHO analgesic ladder
- Changes in measure of tiredness measured by the worst fatigue item (item #3) from the Brief Fatigue Inventory.
- Measures of pain interference specifically evaluating its affect on general activity and sleep as assessed on BPI
- Evaluate the short and long term toxicity to treatment

8.3 Therapeutic Response

Response and progression will be evaluated in this study using a combination of the revised

international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) committee and the guidelines for prostate cancer endpoints developed by the Prostate Cancer Clinical Trials Working Group (PCWG2).

Trial objectives are defined based on controlling, relieving, or eliminating disease manifestations that are present when treatment is initiated. Traditional measures of response reflect when a treatment is working and measures of progression indicate when a drug should be stopped. Because assessing response in bone (the most common site of prostate cancer spread) is uncertain and the clinical significance of PSA changes in response to therapy is not a reliable predictor of response, measures of response have been expanded in consortium trials to include measures of progression.

Patients will need to be reevaluated for response every 12 weeks **±** 1 week during protocol therapy according to the guidelines below.

8.3.1 PSA

Perform PSA testing at a minimum of 1-week intervals with the threshold PSA level at 2.0 ng/mL To report PSA-based outcomes, PCWG2 recommends that the percent of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy) and the maximum decline in PSA that occurs at any point after treatment be reported for each patient using a waterfall plot. Because declines in serum PSA, if they occur, may not do so for several weeks, PSA measurements obtained during the first 12 weeks should not be used as the sole criterion for clinical decision making.

8.3.2 Measurable disease

According to RECIST 1.1, measurable disease is defined as at least 1 lesion ≥ 10 mm in its longest diameter as measured with conventional techniques (i.e., CT or MRI). To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan. All tumor measurements will be taken using a ruler or calipers and recorded in millimeters (or decimal fractions of centimeters).

8.3.3 Nonmeasurable disease

Following RECIST 1.1, all other lesions (or sites of disease) will be considered nonmeasurable disease. This includes small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥10 to <15mm short axis) and any of the following:

- Bone lesions
- Ascites
- Pleural or pericardial effusion
- Lymphangitis cutis or pulmonis
- Abdominal masses that are not confirmed and followed by imaging techniques
- Cystic lesions
- Lesions occurring within a previously irradiated area unless they are documented as new lesions since the completion of radiation therapy

- Leptomeningeal disease

  Note: If only a single, asymptomatic bone lesion is present at baseline, and will be irradiated, the metastatic nature of this lesion must be confirmed by x-ray, CT, or MRI.

8.3.4 Target (nodal and visceral) lesions

Following RECIST 1.1, progression in a nodal or visceral site (i.e., liver and lung) is sufficient to document disease progression. The presence or absence of nodal and visceral disease before and after treatment should be recorded separately.

All measurable lesions (up to a maximum of 2 lesions per organ and 5 lesions in total) will be identified as target lesions to be measured and recorded at baseline. The target lesions should be representative of all involved organs. Target lesions will be selected on the basis of size (i.e., the largest area) and suitability for accurate, repeated measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum of diameters will be used as a reference by which to characterize the objective tumor response.

Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15mm by CT scan.

8.3.5 Bone lesions

On bone scan, progression of bone metastases is defined as the appearance of 2 or more new bone lesions.

•If 2 or more new bone lesions are observed on the first reassessment scan only, a confirmatory scan performed at least 6 weeks later needs to show 2 or more additional new lesions (for a total of 4 or more new lesions since the baseline assessment) for progression to be documented.

• If 2 or more new bone lesions are observed on scans obtained after the first reassessment, a confirmatory scan performed at least 6 weeks later needs to show the persistence of or an increase in the number of bone lesions compared to the prior scan.

The date of progression is always the date of the scan in which the change was first observed.

8.3.6 Nontarget lesions

All other lesions (or sites of disease) will be identified as nontarget lesions and recorded at baseline. Nontarget lesions will include measurable lesions that exceed the maximum number per organ (2) or total of all involved organs (5), as well as nonmeasurable lesions. The presence or absence of these lesions will be recorded on the CRF and should be evaluated at the same assessment time points as all target lesions.

8.3.7 New lesions

The appearance of up to 5 new measurable lesions should be recorded. Each new lesion should be reassessed using the same imaging modality at each time point. If measurable, the diameter of each new lesion should be recorded in the CRF and the sum diameters of new and old lesions should be calculated.

Note: The appearance of a new lesion does not by itself satisfy the criteria for confirmed progressive disease. Rather, the tumor burden imposed by the new lesions must be evaluated within the context of the total tumor burden (i.e., preexisting plus new lesions). Confirming progression in target lesions, non-target (i.e., other than bone) lesions, and bone lesions requires 2 assessment time points. The first must occur at Week 12 (or later) and the second occurring at least 6 weeks after the first. Progression declared at the first time point remains unconfirmed unless assessments at the second time point demonstrate continuing or worsening progression, as described in Section 9.4.

8.4 Response Criteria for Control/Relieve/Eliminate Endpoints

8.4.1. Measurable soft-tissue lesions

When evaluating soft-tissue lesions, the definitions in Table 3 apply.

Table 3 RECIST response criteria for target (soft-tissue) lesions

Response	Evaluation of Soft-Tissue Lesions
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Abbreviations: LD, longest diameter.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (e.g., fine needle aspirate or biopsy) before confirming the complete response status.

Changes in nodal and visceral sites should be recorded and reported separately, and lymph nodes in the pelvis must measure at least 2 cm in greatest diameter to be considered target lesions. Complete elimination of disease at a particular site

should be recorded separately. Any favorable change should be confirmed using a second follow-up scan.

8.4.2 PSA

As long as patient safety is the primary concern, in the absence of other indicators of disease progression, therapy should not be discontinued solely on the basis of a rise in PSA.

For each patient, use a waterfall plot to report the percent change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy) and the maximum decline in PSA that occurs at any point after treatment.

8.4.3 Bone

Record the number of post-treatment lesions. In the absence of clearly worsening soft-tissue (nodal and visceral) disease or disease-related symptoms, progression at the first scheduled assessment should be confirmed on a second scan performed at least 6 weeks later. In the rare case where *visible lesions disappear, this too should be confirmed.*

8.4.4 Non-target lesions

When assessing non-target lesions, the definitions in Table 4 will apply.

Table 4 RECIST response criteria for non-target lesions

Response	Evaluation of Non-target Lesions
Complete response (CR)	The disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis).
Incomplete response/ stable disease (SD)	The persistence of one or more non-target lesions and/or maintenance of tumor marker levels above the normal limits
Progressive disease (PD)	The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

A clear progression of non-target lesions only is exceptional.

8.4.5 Symptoms

BPI short form used to assess pain which includes change in BPI pain severity index, BPI functional interference index. Fatigue based on the BFI will also be used.

8.5 Confirmatory Measures/Duration of Response

8.5.1 Confirming time-to-event outcomes

Any posttreatment change in disease status, be it favorable or unfavorable, should be confirmed using a second assessment at a later time point not less than 6 weeks later.

8.5.2 Duration of overall response

Duration of overall response is measured from the time when partial response or complete response is first noted until the date when recurrent or progressive

disease is objectively documented. Duration of overall complete response is measured from the time the criteria for complete response are first met until the first date that recurrent disease is objectively documented. Duration of stable disease is measured from the start of treatment until the criteria for progression are met.

8.5.3 Progression-free survival

Progression-free survival (PFS) is a composite endpoint defined as the time from study entry or random assignment to disease progression in bone or soft-tissue, symptoms, or death. Use an interval-censored approach in which all assessments of the composite PFS endpoint (i.e., PSA, bone, CT scans, and symptom assessments) are performed at the same time points. All assessments of disease should be collected at the same time interval (e.g., bone scan, CT scan, and PSA at 12-week intervals). In addition to PSA, confirm posttreatment changes in measurable target lesions, radionuclide bone scans, and symptoms.

Table 6 Prostate Cancer Clinical Trials Working Group Outcome Measures[5]

Variable	Control/Relieve/Eliminate Endpoints
PSA	Record the percent change from baseline (rise or fall) at 12 weeks and, separately, the maximal change (rise or fall) at any time using a waterfall plot
Soft-tissue lesions	Use RECIST with caveats: Record changes in nodal and visceral soft tissue sites separately Record complete elimination of disease at any site separately Confirm favorable change with second scan Record changes using waterfall plot
Bone	Record outcome as either *new lesions* or *no new lesions* First scheduled reassessment: No new lesions: continue therapy 2 new lesions: perform a confirmatory scan at least 6 weeks later Confirmatory scan of first reassessment: No new lesions: continue therapy 2 additional new lesions: progression Subsequent scheduled reassessments: No new lesions: continue therapy 2 new lesions: continue therapy and perform a confirmatory scan at least 6 weeks later Confirmatory scan of subsequent reassessments: Lack of persistence of the previously observed new lesions: continue therapy Persistence of or an increase in the number of new lesions: progression
Symptoms	Consider independently of other outcome measures Document pain and analgesia at entry with a lead-in period and measure repeatedly at 3- to 4-week intervals Ignore early changes (~12 weeks) in pain or HRQOL in absence of compelling evidence of disease progression Confirm response or progression of pain or HRQOL endpoints ~3 weeks later

Abbreviations: PSA, prostate-specific antigen; HRQOL, health-related quality of life. †Particularly important when anticipated effect on PSA is delayed or for biologic therapies.

9. DATA REPORTING AND REGULATORY REQUIREMENTS

9.1 Data Collection and Management

Data collected during this study will be entered into a secure database.

9.1.1 Electronic Case Report Forms (eCRFs)

The participating sites will enter data remotely into electronic Case Report Forms (eCRFs) using the internet based PCCTC Caisis Electronic Data Capture (EDC) system. Completion Guidelines will be created by the PCCTC for the collection of all study data. Access and training for PCCTC Caisis EDC will be made available to participating sites upon local regulatory approval. The participating site PI is responsible for ensuring eCRFs are completed accurately and in a timely manner.

9.1.2 Source documents

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation will be made available to support the subject's research record.

9.1.3 Record retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. The investigator will ensure that all regulatory documents and participating site IRB correspondences are maintained in an onsite regulatory binder. After study closure, the investigator will maintain all source documents and study-related documents.. Records are to be retained and securely stored until the later of: (a) two (2) years following the date a New Drug Application is approved for the Study Drug that is the subject of the Clinical Trial; or (b) two (2) years after the Investigational New Drug Application for such Study Drug is terminated or withdrawn, or such longer period of time as may be required by Participant policies, applicable laws, rules or regulations.

9.1.4 Source Documentation Submission for Registration at Participating Sites

Participating sites should email any source documentation that corresponds to data entered at registration to PCCTC at PCCTC@mskcc.org within 24 hours (see Section 4.2.1).

9.1.5 Data Submission Timelines

All study data should be transmitted to PCCTC within 14 days of visit except for SAE submission (see Section 8.3.1) as described in the Data Management Plan.

9.1.6 Data Review and Queries

PCCTC will review data and source documentation as it is submitted. Data will be monitored and source data verified as necessary and discrepancies will be sent as queries to the participating sites. In addition, PCCTC will review data for logic, consistency, and obvious anomalies. Queries will be sent by PCCTC to participating sites as needed.

Participating sites should respond to data queries within 14 days of receipt.

9.2 Study Monitoring and Quality Assurance

9.2.1 Data and Safety Monitoring

The Data and Safety Monitoring Plans (DSMP) at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1. The DSMPs at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC DSMPs can be found on the MSKCC Intranet at: http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf.

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. There are several committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the MSKCC Research Council and Institutional Review Board. As a moderate risk trial, this study will be monitored by DSMC twice per year.

Since therapeutic efficacy is a stated primary objective, all sites participant's responses are subject to review by MSKCC's Therapeutic Response Review Committee (TRRC). Radiology and additional lab reports will need to be obtained from the participating sites for MSKCC TRRC review and confirmation of response assessment. These materials must be sent to MSKCC promptly upon request

9.2.2 Data Auditing and Quality Assurance

In addition to review by DSMC, PCCTC will conduct regularly scheduled remote monitoring every 6 weeks and audits as specified below. Registration reports will be generated by the PCCTC to monitor subject accruals and the completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the Principal Investigator for discussion and action.

Each site participating in the accrual of participants to this protocol will be audited at a minimum of 10% of all subjects, but at least 2 from each site will be 100% source data verified by the PCCTC. Auditing will occur once shortly after initiation of subject recruitment at a site, annually during the study (or more frequently if indicated), and at the end or closeout of the trial, for protocol and regulatory compliance, data verification and source documentation. Audits may be accomplished in one of two ways: (1) sending source documents and research

records for selected patients from participating sites to the PCCTC for audit, or (2) on-site auditing of selected patient records at participating sites.

The audit will include a review of source documentation to evaluate compliance for:

- Regulatory/IRB compliance (review of current protocol and amendments, Informed consent documents and procedures, annual continuing review reports, AEs/SAEs)
- Protocol defined treatment compliance
- Subject records
    1. Each subject is reviewed to determine that there is a signed and dated consent form
    2. Adherence to eligibility criteria
    3. Baseline, on study and follow-up protocol testing
    4. eCRF completion

Audit findings will be reviewed and disseminated to the site PIs and staff.

In addition, each participating site accruing participants to this protocol will be audited by MSK for protocol and regulatory compliance, data verification and source documentation. Audits of selected participant records may be conducted on-site or remotely.

Audits will be conducted annually at minimum, and more often if significant and/or repeated findings are identified during monitoring visits. The number of participants audited will be determined by the outcome of monitoring visits and complexity of the protocol.

Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit. The report will include a summary of findings, participant-specific case review, recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating site must reply within 45 days of receipt of the audit report with their corrective action plan.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

10.1.1 Analysis of the primary endpoint

The primary objective of this phase II study is to determine the effect of Radium-223 on pain improvement for patients with symptomatic metastatic castration-resistant disease. The primary endpoint of the study is a 30% decline in the BPI worst pain item from baseline to week 8, with a confirmed reduction at week 12 without an escalation of the subject's pain regimen from Step 1 to Step 2 or Step 2 to Step 3 of the WHO analgesic ladder. The baseline BPI worst pain score average will be based on the worst pain scores completed by the patient in the 7 consecutive pretreatment days. A minimum of 4 days of pain scores must be completed by the patient in the 7

day window in order to calculate the average worst pain score. We define this event as a response and propose declaring the treatment effective if the probability of a response in the population exceeds 0.20.

A maximum of 63 patients will be entered onto the study. A two-stage design that differentiates between response rates of 0.20 and 0.35 will be used to assess treatment efficacy. In the first stage of the study 27 patients will be enrolled. If at most 5 patients respond, accrual will be terminated. If at least 6 patients respond, an additional 36 patients will be entered onto the study. At the conclusion of this second stage, if at least 17/63 patients respond, the treatment will be declared effective. The probability of declaring the treatment effective is 0.10 when the response rate in the population is 0.20 and increases to 0.90 when the response rate is 0.35.

10.1.2 Analysis of secondary endpoints

A summary of adverse events will be tabulated at baseline and during treatment. Analgesic use will be tabulated, converted into equivalent units, and changes in opiate equivalents before and after treatment will be compared. Descriptive statistics will be used to report the proportion of patients with changes in fatigue scores compared to baseline according to the worst fatigue item (Item #3) of the Brief Fatigue Inventory, at weeks 8 and 12. Descriptive statistics will also be used to report the proportion of patients with changes in pain interference scores compared to baseline based on the interference with activities item of the BPI, at weeks 8 and 12.

The time to radiographic progression and pain progression will be summarized using the cumulative incidence function. The percent change in PSA and bone turnover markers from baseline to 12 weeks will be summarized with descriptive statistics. Longitudinal assessments of BPI, and tiredness will be recorded and summarized over time.

Radiographic progression using PCWG2 criteria for bone scans, and RECIST for soft tissue/measurable disease will be used. The use of FDG PET imaging to demonstrate post-treatment effects is exploratory in nature – the impact of radium on the actual cancer cell is not known. Furthermore, there is no standard method for assessing post-treatment FDG PET changes that have been prospectively validated in prostate cancer. Because Ra-223 is a bone directed agent, bone lesions will be treated separately from soft tissue lesions. We will therefore examine multiple methods of examining post-treatment changes in FDG PET in order to explore which of those will most closely correlate with both pain response. These will include:

A. We will analyze up to 5 bone lesions. Analysis will be performed either on HERMES or AWS workstation. For each lesion, a five point confidence scale will be employed as follows: 1: negative for tumor; 2: probably negative for tumor; 3: equivocal for tumor; 4: probably positive for tumor; 5: definitely positive for tumor. The SUV for each lesion will also be recorded along with its location.

SUVpeak lean body mass will be determined in each of these lesions. The sum of these values at baseline will be compared to that of the sum at followup.

B. If feasible, we will apply the above technique not only to 5 index lesions, but to all of the lesions, using the PET VCAR software or its equivalent.
C. As a comparison, we will explore FDG PET interpretation using the PERCIST 1.0 criteria *(Wahl et al* J Nucl Med 2009 50: 122S-150S).

PSA decline will be reported per PCWG2 criteria [1]

10.2 Analysis Populations

10.2.1 Evaluable population

Responders will be defined by a 30% decline in the BPI worst pain item from baseline to week 8, with a confirmed reduction at week 12 without an escalation of the subject's pain regimen from Step 1 to Step 2 or Step 2 to Step 3 of the WHO analgesic ladder.

Patients with progressive pain will be defined by time until a $\geq$ 2 point increase in the average "worst pain" item on the BPI over a 7 day period compared to baseline is seen and confirmed at least 2 weeks later.

Patients who are neither categorized as pain responders or are categorized as ones with progressive pain will be recorded as non-responders.

All patients who meet eligibility criteria and receive at least 1 dose of study medication will be included in the main analysis of the response rate, even if there are major protocol deviations (e.g., incorrect treatment schedule or drug administration). Each patient will be assigned to one of the above categories.

10.2.2 Safety population

All patients enrolled in the study will be included in the safety analysis population and considered evaluable for toxicity and safety from the time of their first dose. Demographic and baseline characteristics for the safety population will be summarized by number and percent for categorical data (e.g., sex, race/ethnicity) and by descriptive statistics for continuous data (e.g., weight, vital signs, EKG readings, disease status).

10.3 Safety Analysis

10.3.1 Evaluation of adverse events

Pain will be assessed using PBI and fatigue by the BFI.

Treatment-emergent adverse events will be translated from investigator terms to NCI CTCAE v4.0 terminology and summarized (number and percentage of patients) for all patients who receive at least 1 dose. Adverse event summaries will be organized by body system, frequency of occurrence, intensity (i.e., severity grade), and causality or attribution. Patients who experience an adverse event more than once will be counted only once. The occurrence with the maximum severity will be used to calculate intensity.

10.3.2 Evaluation of serious adverse events and premature withdrawals
Adverse events deemed serious and those resulting in treatment withdrawal or death will be summarized separately.

10.3.3 Evaluation of laboratory parameters and assays
Selected clinical laboratory parameters will be summarized and clinically significant changes from baseline will be discussed.

10.3.4 Extent of exposure
Treatment exposure will be summarized for all patients, including dose administration, number of cycles, or delays, and duration of therapy.

11. REGULATORY AND PROTECTION OF HUMAN SUBJECTS

11.1 Roles and Responsibilities

11.1.1 Lead Site/Sponsor Principal Investigator
The Sponsor Principal Investigator at the lead site is responsible for performing the following tasks:

- Responsibility for the overall conduct of the study at all participating sites and for monitoring the progress of the study
- Reviewing and ensuring reporting of Serious Adverse Events (SAEs)
- Reviewing data from all participating sites

11.1.2 PCCTC
The PCCTC is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals and required regulatory documents from each site.
- Managing subject registration
- Developing and maintaining Clinical Data Management documents and procedures
- CRF development, setup of study database, and subsequent design changes
- Participating in review of content of the CRF against the protocol requirements
- EDC system administration (user/site accounts setup, maintenance and revocation)
- Data review, cleaning, query management and resolution
- Establishing procedures for documentation, reporting and submitting of AE's and SAE's to the PCCTC.
- Reviewing Serious Adverse Events (SAEs)
- Training participating sites on EDC
- Collecting and compiling data from each participating site
- Data reviewing from all participating sites
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

11.1.3 Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, the guidelines of Good Clinical Practice (GCP), and applicable Standard Operating Procedures (SOPs). Registering all patients with the PCCTC by submitting the eligibility checklist, supporting source documentation, and signed informed consent promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol
- Maintaining regulatory binders on site and providing copies of all required documents to the PCCTC
- Collecting and submitting data according to the schedule specified by the protocol
- Responding to queries in a timely manner

11.2 Ethical Considerations

This study will be conducted in compliance with the protocol, GCP guidelines established by the International Conference on Harmonisation, and the ethical standards set forth in the Declaration of Helsinki 2004 (available at: www.laakariliitto.fi/e/ethics/helsinki.html).

11.3 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

The following documents must be provided to PCCTC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved informed consent form and HIPAA authorization
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical licenses for each investigator and consenting professional

  Consenting Professionals Lists (consenting professionals at each participating site that may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines)
- Documentation of Human Subject Research Certification training for investigators and key staff members at the participating site
- Documentation of Good Clinical Practice (GCP) training for the PI and co-PI at the participating site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, PCCTC will submit a participating site activation request to MSKCC. Once approved, MSKCC will formally contact PCCTC and grant the site permission to proceed with enrollment.

11.4 Protocol Amendments

Before starting the study, the protocol must be approved by each institution's IRB or Independent Ethics Committee (IEC). Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Once approval of the MSKCC IRB/PB has been granted, PCCTC will distribute all non expedited amendments to the participating sites for submission to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 90 calendar days of MSK IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to PCCTC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

PCCTC is responsible for submitting all participating site local IRB approvals and/or acknowledgments to MSK upon receipt.

11.5 Additional IRB Correspondences

Continuing Review Approval
The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to PCCTC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of new participant enrollment. PCCTC is responsible for submitting all participating site local IRB approvals and/or acknowledgments to MSK upon receipt.

Deviations and Violations
A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSK or a participating site, approval from the MSK IRB/PB is required prior to the action. To request a protocol deviation, participating sites should contact PCCTC who will in turn work with MSK to seek approval from the MSK IRB/PB.

A protocol violation is any change or departure from the research protocol that occurred without prior approval from the MSK IRB/PB. For protocol violations that are identified after they occur, the participating site should report the event(s) to PCCTC as soon as possible. PCCTC will in turn work with MSK to report the violation to the MSK IRB/PB.

Participating sites should report deviations and violations to their institution's IRB as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to PCCTC as received. PCCTC is responsible for submitting all participating site local IRB approvals and/or acknowledgments to MSK upon receipt.

Other correspondence
Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to PCCTC. PCCTC is responsible for submitting all participating site local IRB correspondences to MSK upon receipt

11.6 Written Informed Consent

Before obtaining consent, members of the study team will review the rationale for the treatment program with the patient. The discussion will review the alternatives available (including hormonal therapy, chemotherapy, or supportive care as appropriate), the potential benefits of this program, the risks and the probability of their occurrence, and the procedures to minimize these risks. Should an adverse event occur, the provisions available to ensure medical intervention will also be reviewed. Why the risks are reasonable in relation to the anticipated benefits, incentives, or costs that will or may be incurred as a result of participating in the study, as well as the efforts to maintain confidentiality, will also be discussed with the patient.

Patients will be required to sign and date (in triplicate) a statement of informed consent that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the IRB. The medical record will include a statement that written informed consent was obtained (and document the date that it was obtained) before the patient is enrolled in the study. The original signed document will become part of the patient's medical record, a copy will be forwarded to the lead site/sponsor pursuant to sponsor registration and to the PCCTC and a copy will be sent home with each patient.

The consent form will include the following:

- The nature and objectives, potential toxicities, and benefits of the intended study
- The length of therapy and likely follow-up required
- Alternatives to the proposed therapy (including available standard and investigational therapies)
- The name of the investigator(s) responsible for the protocol
- The right of the patient to accept or refuse treatment and to withdraw from participation in this study
- Text regarding the PCCTC should be added to all institutional informed consent documents and sections in the research authorization/HIPAA forms (e.g., "Prostate Cancer Clinical Trial Consortium")

11.7 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. After this discussion, they will be asked to sign a Notice of Privacy Practice research authorization/HIPAA form. The original signed documents will become part of the patient's medical records, and each patient will receive a copy of the signed documents. The use and disclosure of protected health information will be limited to the individuals described in the research authorization form. The research authorization form must be completed by the principal investigator and approved by the IRB.

11.8 Terminating or Modifying the Study

Adverse event and laboratory data from this trial will be assessed by the lead site or the sponsor's medical monitor on an ongoing basis. SAEs will be reviewed as they are reported to the lead site/sponsor and PCCTC, and the medical monitor will make an assessment regarding the safety of continuing or modifying the study. This assessment will be shared with the investigators either in writing or as part of a teleconference. Should the assessment of either the lead site/sponsor or the principal investigator be that the study should be terminated; the study will be closed to further accrual. Patients who are receiving Ra-223 will be assessed individually by the investigator to see if it is in the patients' best interest to continue, which might be the case for a patient that is responding to the intervention. Follow-up safety assessments will be performed for all patients who are terminated from the study prematurely.

11.9 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld, until the outstanding issues have been resolved.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Description**	**%**	**Description**
0	Normal activity. Fully active, able to continue all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity, minor signs or symptoms of disease
1	Symptoms, but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort, some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed <50% of the time. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most needs
		50	Requires considerable assistance and frequent medical care
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair >50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled, cannot carry on any self-care, totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX B: PCCTC SERIOUS ADVERSE EVENT REPORT FORM

Please see the supplemental PCCTC Serious Adverse Event Report Form

APPENDIX C: GLOSSARY OF ABBREVIATIONS AND ACRONYMS

ADR	adverse drug reaction
ADT	androgen-deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	androgen receptor
ASAEL	Agent Specific Adverse Event List
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
A-V	atrioventricular
BP	blood pressure
BSA	Body Surface Area
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CDE	common data element
CFR	Code of Federal Regulations
CI	confidence interval
Cl-	chloride
CR	complete response
CRC	Clinical Research Center
CRDB	Clinical Research Database
CRF	case report form
CRPC	castration resistant prostate cancer
CT	computerized tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTO	Clinical Trials Office
DEV	deviation from the nominal value
%DEV	percent deviation
dL	deciliter
DLT	dose-limiting toxicity
DSM	data and safety monitoring
EA	extent of absorption
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EEG	electroencephalogram
EKG	electrocardiogram
ESF	eligibility screening form
ESR	expedited safety report
F	bioavailability
FDA	Food and Drug Administration

FDG-PET	2-[18F]fluoro-2-deoxyglucose positron emitting tomography
FDHT	18-fluoro-dehydrotestosterone
GCP	good clinical practice
GCPII	glutamate carboxypeptidase II enzyme
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GnRH	gonadotropin-releasing hormone
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
HRPC	hormone-refractory prostate cancer
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunochemical
IM	intramuscular
IND	investigational new drug
INR	international normalized ratio
IP	intraperitoneal
IRB	Institutional Review Board
ITT	intent-to-treat population
IV	intravenous
LD	longest diameter
LDH	lactate dehydrogenase
LOI	letter of intent
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
MS	mass spectrometry
MTD	maximum tolerated dose
N	number of subjects or observations
NA	not applicable
N/A	not available
NBN	National Biospecimen Network
NCI	National Cancer Institute
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NSAID	nonsteroidal anti-inflammatory drug
NTX	N-telopeptide cross-link
NVB	neurovascular bundle
OCR	Office of Clinical Research at MSKCC
PCCTC	Prostate Cancer Clinical Trials Consortium
PCRP	Department of Defense Prostate Cancer Research Program
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival

PI	principal investigator
PIN	prostatic intraepithelial neoplasia
PK	pharmacokinetics
PMB	Pharmaceutical Management Branch
PO	per os (by mouth)
PR	partial response
PRO	Patient Reported Outcome
PSA	prostate-specific antigen
PSA-DT	prostate-specific antigen doubling time
PSMA	prostate specific membrane antigen
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
qd	quaque die (every day)
qRT-PCR	quantitative reverse transcription-polymerase chain reaction
QOL	quality of life
RBC	red blood cell
RC	Research Council
RDRC	Radioactive Drug Research Committee
RECIST	Response Evaluation Criteria in Solid Tumors
RP	radical prostatectomy
RPC	Research Program Coordinator
RSA	Research Study Assistant
%RSD	percent relative standard deviation
SAE	serious adverse event
SD	standard deviation
SD	stable disease
SKI	Sloan-Kettering Institute for Cancer Research
SMD	stable metabolic disease
SOP	Standard Operating Procedures
SUV	standardized uptake value
t	temperature
t1/2	terminal half-life
T	time
TDP	time to disease progression
TGP	prostate-specific transglutaminase
tid	ter in die (3 times a day)
TMA	tissue microarray
Tmax	time of maximum observed concentration
TMPRSS2	transmembrane protease, serine 2
TNM	tissue, lymph node, metastases
TX	treatment
ULN	upper limit of normal
ULQ	upper limit of quantitation
UR	urinary recovery
VEGF	vascular endothelial growth factor
Vss	volume of distribution at steady-state

WBC	white blood cell
WHO	World Health Organization

APPENDIX D: DOSIMETRY

Dosimetry for Ra-223 dichloride

Target Organ	Mean (Rad/mCi)	SINGLE TREATMENT Rad/ 0.0946 mCi	6 TREATMENTS Rad/0.568 mCi
Adrenals	0.44	0.04	0.25
Brain	0.37	0.04	0.21
Breasts	0.18	0.02	0.10
Gallbladder wall	0.85	0.08	0.48
LLI1 Wall	171.88	16.26	97.56
Small Intestine Wall	26.87	2.54	15.25
Stomach Wall	0.51	0.05	0.29
ULI2 wall	119.58	11.31	67.87
Heart wall	6.40	0.61	3.63
Kidneys	11.86	1.12	6.73
Liver	11.01	1.04	6.25
Lungs	0.27	0.03	0.15
Muscle	0.44	0.04	0.25
Ovaries	1.80	0.17	1.02
Pancreas	0.41	0.04	0.23
Red Marrow	513.51	48.58	291.47
Osteogenic cells	4262.60	403.24	2419.45
Skin	0.27	0.03	0.15
Spleen	0.33	0.03	0.19
Testes	0.31	0.03	0.18
Thymus	0.21	0.02	0.12
Thyroid	0.26	0.02	0.15
Urinary Bladder Wall	14.90	1.41	8.46
Uterus	0.94	0.09	0.53
Whole body	85.50	8.09	48.53

based on package insert
*typical dose 70 kg at 1.3514 mCi/kg

APPENDIX E: BRIEF FATIGUE INVENTORY[14]

Please see attached supplemental Brief Fatigue Inventory survey.

APPENDIX F: BRIEF PAIN INVENTORY

Please see attached supplemental Brief Pain survey.

APPENDIX G: RADIATION SAFETY PRECAUTIONS FOLLOWING RADIUM-223 DICHLORIDE, INJECTION

You will be given a card which informs people that you have received radioactive medicine, always carry this card with you.

There are NO restrictions regarding contact with other people after receiving the study drug.

During the first week after Radium-223 Dichloride injection there may be some radioactivity in your blood, urine, and stools, therefore you should take the following precautions:

- Use medical gloves when wiping up blood, urine, stools, or vomit, or when handling stained clothes.
- A normal toilet should be used in preference to a urinal. The sitting position should be used instead of the standing position.
- Wipe up any spilled urine or stool with a tissue and flush it away.
- If you are sick, wipe up spilled vomit with a tissue and flush it away.
- Ensure that you always thoroughly wash your hands after using the toilet or after wiping up spilled fluids.
- Wash any linen or clothes that become stained with urine, blood or stools separately from other clothes and rinse them thoroughly.
- If you are sexually active, the use of a condom is recommended during the first week after injection because there may be some slight radioactivity in the body fluids (but most in blood, urine and stools).
- If sampling of blood, urine or stools is necessary during the first week following administration, please inform the personnel that you have been treated with radioactive Radium-223.
- If you need medical care such as an operation or hospital admission during the first week following administration, please inform the personnel that you have been treated with radioactive Radium-223.

Radiation Safety Service
Memorial Sloan-Kettering Cancer Center
Telephone: 1-212-639-7391

APPENDIX H: PRO INSTRUMENT SCREENSHOT

Please see attached supplemental PRO Instrument Screenshot.

APPENDIX I: PRO INSTRUMENT INSTRUCTIONS

Please see attached supplemental PRO Instrument Instructions.

APPENDIX J: RADIUM DOSE TRACKING SHEET (MSK SITE ONLY)

Please see attached supplemental Radium Dose Tracking Sheet.