A Phase 2 study of Radium-223 and Radiotherapy in Hormone-Naïve Men with Oligometastatic Prostate Cancer to bone
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events

Abbreviation or Term[1]	Definition/Explanation
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli gratia (for example)
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional review board

Abbreviation or Term[1]	Definition/Explanation
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LLQ	Lower limit of quantitation
MedRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine

Abbreviation or Term[1]	Definition/Explanation
T_{max}	Time of maximum observed concentration
TID	Three times daily
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

STUDY SUMMARY

Title	A Phase 2 study of Radium-223 and Radiotherapy in Hormone-Naïve Men with Oligometastatic Prostate Cancer to bone
Short Title	Radium-223 and Radiotherapy for Oligometastatic ProstatE cancer (RROPE)
Protocol Number	IRB #102312
IND	IND Exempt
Phase	Phase IIA
Design	Prospective, single arm, non-randomized, non-blinded open label study of Radium-223 and radiotherapy in men with oligometastatic prostate cancer to bone
Study Duration	3-4 years (accrual at 2 patients per month. Study duration 6 months per patient. 2 year follow up.)
Study Center(s)	This is a single site study conducted at the Huntsman Cancer Institute
Objectives	Primary Objective: Freedom from Androgen Deprivation Therapy (ADT) or other antineoplastic systemic at 15 months. Secondary Objective: QOL assessments, Progression Free Survival, Overall Survival
Number of Subjects	20
Diagnosis and Main Eligibility Criteria	Men with Prostate Cancer and no more than 5 sites of bony metastatic disease without visceral involvement.
Study Product, Dose, Route, Regimen	• Radium-223 55 kBq (1.49 mCi)/kg (+/- 10% total dose) at study enrollment, and then every 4 weeks following definitive radiation therapy for a total of six Radium-223 infusions. • Hypofractionated Radiotherapy to all oligometastatic sites
Duration of administration	6 months of therapy
Reference therapy	Institutional Care Standard (99% of subjects starting Androgen Deprivation Therapy by 15 months)

Statistical Methodology	Assess the proportion of ADT naïve men who progress and require ADT at 15 months.

1 OBJECTIVES

We hypothesize that treatment with Radium-223 and focal radiotherapy to 5 or fewer sites of clinically detectable bony metastases will delay the time to start systemic therapies (androgen deprivation therapies (ADT) or other antineoplastic systemic therapies). This hypothesis will be tested through the following aims.

1.1 Primary Objectives and Endpoint

1.1.1 Determine if 20% of ADT naïve men treated with concurrent EBRT and Radium-223 will not require ADT for progression by 15 months.
Endpoint: Determine the time from start of study therapy to start of ADT.

1.2 Secondary Objectives and Endpoint

1.2.1 Determine the hormone-therapy free survival time for men treated with concurrent EBRT and Radium-223 and determine whether it is a 30% risk reduction over the SWOG intermittent ADT historic cohort
Endpoint: Determine the time from start of study therapy to start of ADT.

1.2.2 Evaluate health-related quality of life (QOL) as scored by the 50-item Expanded Prostate Inventory Composite (EPIC) EPIC urinary, bowel, sexual, and hormonal domains. The PROMIS 29 will be used to assess general function and well-being
Endpoint: The PROMIS 29 will be used to assess general function and well-being.

1.2.3 Evaluate time to first skeletal related event (SRE)
Endpoint: Documentation of complications associated with bone metastases and may include (but not limited to) fractures, spinal cord compression, bone pain, and hypercalcemia.

1.2.4 Evaluate the PSA doubling time
Endpoint: Time elapsed from baseline PSA to double in value.

1.2.5 Evaluate overall survival at 2 years relative to the SWOG intermittent ADT historic cohort.
Endpoint: Patients will be followed for survival for two years after study enrollment

1.2.6 Evaluate CTCAE version 4.0 toxicities in the study population
Endpoint: Patients will be monitored for adverse events related to Radium-223 and EBRT using CTCAE criteria.

1.3 Exploratory Objectives

1.3.1 Evaluate whether a commercially available cell-cycle progression gene assay (Myriad CCP) performed on the original prostate biopsy or surgical pathology specimen correlates with biochemical or clinical progression free survival in the study population.

1.3.2 Evaluate whether a commercially available homologous recombination DNA repair assay correlates with biochemical or clinical progression free survival in the study population (Myriad HRD).

2 BACKGROUND

Background: Prostate cancer is the most commonly diagnosed cancer in the United States and second leading cause of cancer death. At diagnosis, approximately 10% of men will have bone metastases identified on technetium bone scan [1]. These bone metastases can result in skeletal related events (SREs) causing substantial morbidity [2]. Men with five or fewer prostate cancer bone metastases noted on initial bone scan have a 94% 2-year survival rate, and a significantly favorable overall survival when compared to those with more lesions [3]. The current standard of care for men with overt metastatic disease is immediate androgen deprivation therapy (ADT) [4]. Long term androgen deprivation therapy results in a significant decrement in quality of life[5] and a host of unfavorable side effects including but not limited to loss of libido, lack of energy, difficulty concentrating, hot flashes, decreased bone density, decreased muscle mass, and increased risk of heart attack and stroke. Although ADT will delay the appearance of tumor related symptoms in metastatic patients, there are no data that it prolongs overall survival[4]. Developing novel strategies to control metastatic prostate cancer with side effect profiles superior to that of ADT or other approved systemic agents is highly desirable. External beam radiation treatment is effective at controlling both primary and metastatic prostate cancers, and Radium-223 has demonstrated a survival benefit in castrate-resistant prostate cancers. Both forms of therapy have been shown to palliate painful bony lesions.

Rationale for the combination of Radium-223 and External Beam Radiation: Radium-223 is a calcium-mimetic radiopharmaceutical that accumulates in bones and emits alpha radiation from Radium-223 decay and releases relatively high energy with a narrow range (2 to 10 cells)[5]. Following promising results in a phase II trial, the phase III ALSYMPCA trial was conducted in mCRPC with symptomatic bone metastases who either had received or were ineligible for docetaxel [6, 7]. Patients received 6 doses of Radium-223 50 kBq/kg intravenously every 4 weeks. A pre-planned interim analysis showed a significant 2.8-month median OS benefit compared to the placebo arm (14 vs. 11.2 months), which is anticipated to lead to regulatory approval [8]. An updated analysis

showed a further improvement in overall survival to 3.6 months with a hazard ratio of 0.695 (i.e., 30.5% reduction in risk of death) [9]. Moreover, the toxicity profile appeared excellent with grades 3-4 neutropenia in 1.8% and thrombocytopenia in 4% of patients. Reassuringly, long-term, 24-month outcomes in the previous randomized phase II trial showed no increase in hematologic toxicities [6, 7].

Radiotherapy for Oligometastasis: In 1995, Hellman and Weichselbaum coined the term "oligometastases" to characterize a state of limited metastasis in which aggressive local control measures could be potentially curative [10, 11]. This led to the development of prospective clinical trials employing the use of Stereotactic Body Radiotherapy (SBRT) to ablate visible oligometastatic disease with curative intent [12]. This approach has been demonstrated to be safe and effective, with local control rates in the 80% range, and durable progression-free survival rates around 20%. In one of the only trials evaluating the role of SBRT exclusively in 40 patients with bone only metastatic prostate cancer, the actuarial 24-month local tumor control rate was 95.5% as measured by MRI and PET CT imaging and the median initial PSA before treatment was 5.4 ng/dl which dropped to 2.7 ng/dl after 3 months [13]. We propose that the combination of external beam radiotherapy and Radium-223 will be an effective therapy at controlling oligometastatic prostate cancer in hormone-therapy naïve patients.

Comparator Cohort:

At the Huntsman Cancer Institute at the University of Utah, 100% of persons have been started on systemic therapies to treat their metastatic prostate cancer by 15 months of the identification of oligometastasis. The goal of the current study is to assess whether the Radium-223 and EBRT to oligometastatic sites will delay the need to initiate additional antineoplastic systemic therapies by 15 months.

Other Comparators of interest that are not specified as the primary aim:

In 2012 the SWOG cooperative group reported mature results of a randomized trial evaluating continuous versus intermittent androgen-deprivation therapy in men with hormone-naïve metastatic prostate cancer [14]. This trial was pivotal in cementing the care standard of immediate and continuous androgen deprivation in men with hormone-naïve metastatic prostate cancer, as a median survival benefit was noted over the intermittent cohort despite the fact that, statistically speaking, inferiority of intermittent therapy was not proven nor disproven. Men on the intermittent therapy arm did have significant improvement in quality of life domains. Notably, **78%** of persons on the "intermittent" androgen therapy arm had to resume ADT within the first 15 months**.** Additionally, the investigators of this study classified patients as having "minimal" versus "extensive" disease as an analysis stratification. Minimal disease was defined as disease confined to the spine, pelvic bones, or lymph nodes. Those with visceral metastasis or other bony sites were classified as extensive. At 2 years, subjects with "minimal disease" receiving intermittent androgen deprivation had an **85%** overall survival. We propose using the intermittent ADT cohort of the SWOG trial as a historic comparator of efficacy to this study.

Oligometastasis is a limited disease state that some have postulated may by curable. We will use best available ablative therapies to destroy gross tumor, and allow radium--223 to obliterate occult sites of metastasis that cannot be resolved by available imaging modalities. This may lead to delay of initiation of ADT or other antineoplastic systemic therapies, improved QOL, survival benefit, and potential cure.

Reference treatment is the standard of care use of immediate and continuous ADT as well as other reasonable standards of intermittent ADT, or other antineoplastic systemic therapies. Hypofractionated radiotherapy is not routinely used in asymptomatic lesions unless there is risk of impending pathologic injury.

3 DRUG AND RADIATION THERAPY INFORMATION

3.1 Radium Ra-223 (Drug information for Radium-223 taken from the investigators brochure and Xofigo prescribing information.

3.1.1 Description

Radium Ra-223 dichloride, an alpha particle-emitting pharmaceutical, is a radiotherapeutic drug. Radium Ra-223 dichloride is supplied as a clear, colorless, isotonic, and sterile solution to be administered intravenously with pH between 6 and 8. Each milliliter of solution contains 1100 kBq Radium-223 dichloride (30 microcurie), corresponding to 0.58 ng radium-- 223, at the reference date. Radium is present in the solution as a free divalent cation. Each vial contains 6 mL of solution (6,600 kBq (178 microcurie) Radium-223 dichloride at the reference date). The inactive ingredients are 6.3 mg/mL sodium chloride USP (tonicity agent), 7.2 mg/mL sodium citrate USP (for pH adjustment), 0.2 mg/mL hydrochloric acid USP (for pH adjustment), and water for injection USP. The molecular weight of Radium-223 dichloride, 223RaCl2, is 293.9 g/mol. Radium-223 has a half-life of 11.4 days. The specific activity of Radium-223 is 1.9 MBq (51.4 microcurie)/ng. The six-stage-decay of Radium-223 to stable lead-207 occurs via short-lived daughters, and is accompanied predominantly by alpha emissions. There are also beta and gamma emissions with different energies and emission probabilities. The fraction of energy emitted from Radium-223 and its daughters as alpha-particles is 95.3% (energy range of 5 - 7.5 MeV). The fraction emitted as beta-particles is 3.6% (average energies are 0.445 MeV and 0.492 MeV), and the fraction emitted as gamma-radiation is 1.1% (energy range of 0.01 - 1.27 MeV).

NIST Standardization

The quantification of Radium-223 radioactivity 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 (as provided in the Investigator Brochure). 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 (as provided in the Investigator Brochure) and results obtained by other national metrology institutes (United Kingdom, Germany, Japan). After completion of the re-assessment, NIST reported their findings (ss provided in the Investigator Brochure) 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 current NIST standard for Radium-223 dichloride remained in effect until 4/25/16. As of that date the FDA approved the regulatory variation submitted for Radium-223. 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 Radium-223. 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 is being updated to reflect the new standard. The current dose regimen of Radium-223 is 55 kBq (1.49 microcurie) per kg body weight.

3.1.2 Mechanism of Action

The active moiety of Radium Ra-223 dichloride is the alpha particle-emitting isotope Radium-223 (as radium Ra-223 dichloride), which mimics calcium and forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases. The high linear energy transfer of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in an anti-tumor effect on bone metastases. The alpha particle range from Radium-223 dichloride is less than 100 micrometers (less than 10 cell diameters) which limits damage to the surrounding normal tissue.

3.1.3 Preclinical

In single and repeated dose toxicity studies in rats, the main findings were reduced body weight gain, hematological changes, reduced serum alkaline phosphatase and microscopic findings in the bone marrow (depletion of hematopoietic cells, fibrosis), spleen (secondary extra-medullary hematopoiesis) and bone (depletion of osteocytes, osteoblasts, osteoclasts, fibro-osseous lesions,

disruption/disorganization of the physis/growth line). These findings were related to radiation-induced impairment of hematopoiesis and a reduction of osteogenesis and occurred beginning in the dose range of 20 (0.00056 mCi) – 80 kBq (0.0022 mCi) per kg body weight, with the exception of body weight decreases.

Dose-limiting myelotoxicity was seen in dogs after single administration of 450 kBq (0.012 mCi) Radium Ra-223 dichloride per kg body weight (9 times the clinically recommended dose).

Osteosarcomas, a known effect of bone-seeking radionuclides, were observed at clinically relevant doses in rats 7 to 12 months after start of treatment. Osteosarcomas were not observed in dog studies. The presence of neoplastic changes, other than osteosarcomas, was also reported in the longer term (12 to 15 months) rat toxicity studies. Due to its mode of action, and as seen with conventional radiotherapy and other radiotherapeutics, Radium-223 dichloride may have the potential to induce secondary malignancies. No case of osteosarcoma has been reported in clinical studies with Radium Ra-223 dichloride. The risk for patients to develop osteosarcomas with exposure to Radium Ra-223 dichloride is unknown at present.

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

No histological changes were observed in organs involved in the excretion of Radium Ra-223 dichloride. No significant effects were seen on vital organ systems, i.e., cardiovascular (dog), respiratory or central nervous systems (rat), after single dose administration of 450 to 1000 kBq (0.012 to 0.027 mCi) per kg body weight (9 (dog) to 20 (rat) times the clinically recommended dose.

3.1.4 Clinical Experience Summary

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

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

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

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

The results of both, interim and updated analysis, revealed that OS was significantly longer in patients treated with Radium Ra-223 dichloride plus best standard of care compared to patients treated with placebo plus best standard of care. For the updated analysis, an increase in median overall survival of 3.6 months was seen with Radium Ra-223 dichloride plus best standard of care compared to placebo plus best standard of care (HR =0.695 (95% CI 0.581/0.832), median OS 14.9 months versus 11.3 months, respectively).

In the ALSYMPCA study, the results of the interim analysis and the updated analysis showed also a significant improvement in all main secondary endpoints in the Radium Ra-223 dichloride arm compared to the placebo arm:

- Time to first SRE (defined as time to EBRT, time to first pathological bone fracture, time to spinal cord compression and time to surgical intervention) was statistically significantly longer in the Radium-223 chloride group compared to placebo (median number of months=15.6 for Radium-223 chloride versus 9.8 months for placebo (HR=0.658, 95 CI 0.522–0.830, p= 0.00037).
- Time to total ALP progression (defined as ≥ 25% increase compared to baseline/nadir) was statistically significantly longer in the Radium-223 chloride group 7.4 months compared to placebo 3.8 months (HR = 0.167, 95% CI 0.129 – 0.217; p= <0.00001).
- Time to PSA progression (defined as a ≥ 25% increase and an increase in absolute value of ≥ 2 ng/mL compared to baseline/nadir) was also significantly prolonged in patients receiving Radium Ra-223 dichloride compared to patients receiving placebo (HR = 0.643, 95% CI 0.539,0.768; p = <0.00001)
- A total ALP response (defined as a confirmed ≥ 30% or ≥ 50% reduction compared to baseline) at week 12 was observed in higher proportions of subjects who were treated with Radium-223 chloride group (47% and 3% respectively) compared to those in the placebo (3% and <1% respectively) group.
- Subgroup survival analysis showed a consistent survival benefit for treatment with Radium Ra-223 dichloride, independent of total alkaline phosphatase (ALP), current use of bisphosphonates, prior use of docetaxel and baseline ECOG status. The results from the phase III ALSYMCA study regarding time to external beam radiation therapy (EBRT) for pain relief and fewer patients reporting bone pain as

an adverse event in the Radium Ra-223 dichloride group indicate a positive effect on bone pain.

The most common adverse reactions (≥ 10%) in patients receiving Radium Ra-223 dichloride were nausea, diarrhea, vomiting, and peripheral edema (Table 2.1). Grade 3 and 4 adverse events were reported among 57% of Radium Ra-223 dichloride-treated patients and 63% of placebo treated patients. The most common hematologic laboratory abnormalities in Radium Ra-223 dichloride-treated patients (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia (Table 2.2). Treatment discontinuations due to adverse events occurred in 17% of patients who received Radium Ra-223 dichloride and 21% of patients who received placebo.

The most common hematologic laboratory abnormalities leading to discontinuation for Radium Ra-223 dichloride were anemia (2%) and thrombocytopenia (2%).

Table 2.1 shows adverse reactions occurring in ≥ 2% of patients and for which the incidence for Radium Ra-223 dichloride exceeds the incidence for placebo.

Table 2.1: Adverse Reactions in the Randomized Trial

System/Organ Class Preferred Term	Radium Ra-223 dichloride (n=600)		Placebo (n=301)	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Blood and lymphatic system disorders				
Pancytopenia	2	1	0	0
Gastrointestinal disorders				
Nausea	36	2	35	2
Diarrhea	25	2	15	2
Vomiting	19	2	14	2
General disorders and administration site conditions				
Peripheral edema	13	2	10	1
Renal and urinary disorders				
Renal failure and impairment	3	1	1	1

Laboratory Abnormalities

Table 2.2 shows hematologic laboratory abnormalities occurring in > 10% of patients and for which the incidence for Radium Ra-223 dichloride exceeds the incidence for placebo.

Table 2.2: Hematologic Laboratory Abnormalities

Laboratory values were obtained at baseline and prior to each 4-week cycle.

Hematologic	Radium-223 (n=600)		Placebo (n=301)	
Laboratory	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Abnormalities	%	%	%	%
Anemia	93	6	88	6
Lymphocytopenia	72	20	53	7
Leukopenia	35	3	10	<1
Thrombocytopenia	31	3	22	<1
Neutropenia	18	2	5	<1

As an adverse reaction, grade 3-4 thrombocytopenia was reported in 6% of patients on Radium Ra-223 dichloride and in 2% of patients on placebo. Among patients who received Radium Ra-223 dichloride, the laboratory abnormality grade 3-4 thrombocytopenia occurred in 1% of docetaxel naïve patients and in 4% of patients who had received prior docetaxel. Grade 3-4 neutropenia occurred in 1% of docetaxel naïve patients and in 3% of patients who have received prior docetaxel.

Fluid Status

Dehydration occurred in 3% of patients on Radium Ra-223 dichloride and 1% of patients on placebo. Radium Ra-223 dichloride increases adverse reactions such as diarrhea, nausea, and vomiting which may result in dehydration.

Injection Site Reactions

Erythema, pain, and edema at the injection site were reported in 1% of patients on Radium Ra-223 dichloride.

Secondary malignant neoplasms

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

Bone Marrow Suppression

In the randomized trial, 2% of patients on the Radium Ra-223 dichloride arm experienced bone marrow failure or ongoing pancytopenia compared to no patients treated with placebo. There were two deaths due to bone marrow failure and for 7 of 13 patients treated with Radium Ra-223 dichloride, bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients on the Radium Ra-223 dichloride arm and 2% on the placebo arm permanently discontinued therapy due to bone marrow suppression.

In the randomized trial, deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Radium Ra-223 dichloride-treated

patients compared to 0.3% of patients treated with placebo. The incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (<1%) were similar for patients treated with Radium Ra-223 dichloride and placebo.

Myelosuppression; notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia; has been reported in patients treated with Radium Ra-223 dichloride. In the randomized trial, complete blood counts (CBCs) were obtained every 4 weeks prior to each dose and the nadir CBCs and times of recovery were not well characterized. In a separate single-dose phase 1 study of Radium Ra-223 dichloride, neutrophil and platelet count nadirs occurred 2 to 3 weeks after Radium Ra-223 dichloride administration at doses that were up to 1 to 5 times the recommended dose, and most patients recovered approximately 6 to 8 weeks after administration.

In the Radium-233 arm of the Phase 3 clinical trial reported in Parker et al. (2013) 12.7% (76/600) of subjects had grade 3+ anemia, 6.5% (39/600) of subjects had grade 3+ thrombocytopenia, and 2.2% (13/600) of subjects had grade 3+ neutropenia.

The safety and efficacy of concomitant chemotherapy with Radium Ra-223 dichloride have not been established. Outside of a clinical trial, concomitant use with chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes or hemibody external radiotherapy are administered during the treatment period, Radium Ra-223 dichloride should be discontinued.

3.2 **External beam radiation therapy**

Radiation therapy will be performed on linear accelerators capable of delivering X-ray or electron therapy in the 4MeV to 18 MeV range with image guidance systems.

4 STUDY DESIGN

4.1 Description

This is a phase IIa, open-label, single-arm, and prospective study of hormone therapy-naïve men with oligometastatic prostate cancer to the bone. The study will test if treating the primary tumor sites and 5 or fewer sites of bone-only metastasis with external beam radiation with concomitant systemic Radium-223 will reduce the utilization of androgen deprivation therapy, improve QOL and improve OS over the comparator cohort of SWOG intermittent ADT historic cohort.

4.2 Number of Patients

20 patients

4.3 Number of Study Centers

This study will be conducted at a single site, the Huntsman Cancer Institute

4.4 Study Duration

The estimated duration for the protocol (from start of screening to last subject processed and finishing the study) is 3 to 4 years (Accrual at 2 patients per month. Study duration will be 6 months per patient. Patient will be followed for approximately 2 years after study enrollment).

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with signature in the patient research chart.

Patient No. _____
Patient's Initials: (L, F, M) _____

5.1 Inclusion Criteria

Yes/No (Response of "no" = patient ineligible)

5.1.1 _____ Asymptomatic or symptomatic hormone naïve men with testosterone levels ≥100 ng/dL with previously treated localized prostate cancer who now have rising PSAs and five or fewer bone metastases.

5.1.2 ____ Subjects who have been previously treated with definitive and/or adjuvant/salvage radiotherapy to the primary site and/or regional lymph nodes with concurrent ADT are allowed if the last hormone therapy delivered > 6 months prior. Subjects who have had more than 30 days and fewer than 45 days of bicalutamide monotherapy for any reason within the 6 months prior to enrollment are eligible for the study, providing they have been off of the drug for at least 30 days prior to enrollment. Subjects who have had fewer than 30 days of bicalutamide are eligible for the study, as long as they discontinue the drug at least 5 days prior to the first study treatment.

5.1.3 _____ Histologic confirmation of Prostate Adenocarcinoma diagnosis.

5.1.4 _____ Age ≥ 18 years.

5.1.5 _____ Life expectancy of at least 2 years.

5.1.6 _____ Acceptable hematology and serum biochemistry screening values:

- White Blood Cell Count (WBC) ≥ 3,000/mm3
- Absolute Neutrophil Count (ANC) ≥ 1,500/mm3
- Platelet (PLT) count ≥ 100,000/mm3
- Hemoglobin (HGB) ≥ 10 g/dl
- Total bilirubin level ≤ 1.5 x institutional upper limit of normal (ULN)
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
- Creatinine ≤ 1.5 x ULN
- Albumin > 2.5 mg/dL

5.1.7 _____ Willing and able to comply with the protocol, including follow-up visits and examinations.

5.1.8 _____ Karnofsky Performance Score >60 or ECOG equivalent.

5.1.9 _____ Radiographic confirmation of oligometastatic diagnosis via Bone Scan validated by either CT scan, or MRI or PET/CT with Fluciclovine within the past 90 days.

5.1.10 _____ Subjects who have not had surgical removal of their prostate and have a partner of child bearing potential must agree to use condoms beginning at the signing of the ICF until at least 6 months after the last dose of study drug. Because of the potential side effect on spermatogenesis associated with radiation, female partners of childbearing potential must agree to use a highly effective contraceptive method during and for 6 months after completing treatment.

5.1.11 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.2 **Exclusion Criteria**

Yes/No (Response of "yes" = patient ineligible)

5.2.1 _____ Men with known brain or visceral metastases (except regional lymph nodes as defined by section 5.2.5) defined by CT or MRI Imaging of the abdomen or pelvis.

5.2.2 _____ Men who have had LHRH agonist or antagonist hormone therapy in the prior six months.

5.2.3 _____ Men with >5 validated bony metastases.

5.2.4 _____ Men with baseline serum Testosterone <100 ng/dL.

5.2.5 _____ Men with new or progressing lymphadenopathy clearly consistent with prostate metastasis on imaging or proven by pathologic biopsy at any time three months or later following their initial definitive therapy.

5.2.6 _____ Prior or concurrent invasive malignancy (except non-melanomatous skin cancer) or lymphomatous/hematogenous malignancy unless continually disease free for a minimum of 3 years. All patients with in situ carcinoma are eligible for this study (for example, carcinoma in situ of the oral cavity is eligible) except patients with carcinoma of the bladder (including in situ bladder cancer or superficial bladder cancer).

5.2.7 _____ Use of finasteride within 30 days prior to therapy PSA should not be obtained prior to 30 days after stopping finasteride.

5.2.8 _____ Use of dutasteride within 90 days prior to therapy. PSA should not be obtained prior to 90 days after stopping dutasteride.

5.2.9 _____ Previous or concurrent cytotoxic chemotherapy for prostate cancer.

5.2.10 _____ Received systemic therapy with radionuclides (e.g., strontium-89, samarium-153, rhenium-186, or rhenium-188, or Radium Ra-223 dichloride) for the treatment of bony metastases.

5.2.11 _____ Men who will receive radical prostatectomy to the primary site.

5.2.12 _____ Imminent spinal cord compression based on clinical findings and/or magnetic resonance imaging (MRI). Spinal Cord compression will be defined as 360-degree circumferential obliteration of T2 cerebrospinal fluid signal around the spinal cord. Treatment should be completed for spinal cord compression.

5.2.13 _____ Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol. (Patients on Coumadin or other blood thinning agents are eligible for this study.)
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

5.2.14 _____ Cardiac failure New York Heart Association (NYHA) III or IV Crohn's disease or ulcerative colitis.

5.2.15 _____ Bone marrow dysplasia.

5.2.16 _____ Fecal incontinence.

5.2.17 _____ Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

_____	_____	_____
Investigator Signature	**Date**	**Time**

6 STRATIFICATION

Not Applicable: This study will consist of subjects initially diagnosed with M0 prostate cancer at presentation who have completed definitive treatment to the prostate, seminal vesicles, and regional lymph nodes (if applicable), who then later developed oligometastatic disease.

7 TREATMENT GUIDELINE

7.1 External Beam Radiation Administration Schedule

7.1.1 All external beam radiations oligometastatic sites will commence after cycle one of Radium-223 but prior to cycle two of Radium-223.

7.1.1.1 All lesions seen on bone scan and corroborated by the validating scans will be treated. If there are additional suspicious bone lesions seen on Bone scan, CT, MRI, PET/CT, or treatment-planning simulation scans, but not corroborated by a second scan, they can be targeted at the treating physician's discretion as long as no more than 5 lesions total are targeted with external beam radiation.

7.1.2 External Beam radiation for Oligometastasis

7.1.2.1 **Dose Specification**

All subjects will receive Stereotactic body or hypofractionated radiation to sites of bone disease seen on imaging studies using any one of the isoequivalent radiation regimens (based on the linear quadratic model with EQD2=60gy and an alpha/beta ration for prostate cancer= 2). EQD2 (equivalent radiobiological dose if converted to 2Gy daily fractions) is being utilized to allow the radiation oncologist the flexibility to give an ablative dose to tumor but allow for differing regimens to spare critical normal tissues depending on tumor location.

Any of the following regimens are considered ablative, acceptable, and are biologically equivalent to 60Gy EQD2:

- Single fraction: 16 Gy total at 16 Gy per fraction (SBRT)
- Three fractions: 24 Gy total at 8 Gy per fraction (SBRT)
- Five fractions: 30 Gy total at 6 Gy per fraction (SBRT). When using five fractions, can reduce to 25 Gy total at 5 Gy per fraction (SBRT) or to a minimum of 20 Gy total at 4 Gy per fraction (SBRT), per treating investigator.
- Six fractions: 32.4 Gy total at 5.4Gy per fraction (Hypofractionated)

If any of the fractions need to be further reduced, this can be done in consultation with the medical monitor.

7.1.2.2 Target Localization

This study requires the use of IGRT. NRG Oncology defines IGRT as a computer-assisted process that uses imaging devices that generate a series of coordinates for shifting the patient support system in three orthogonal directions (sometimes including rotational changes) to position the treatment beams relative to target regions. The allowed technologies are as follows: cone-beam CT (CBCT) using either a specially mounted kV imaging head or the MV treatment beam with an opposed electronic imaging panel, dual fixed-position in-room kV imaging systems that are orthogonal or near orthogonal, an in-room standard diagnostic CT scanner that is geometrically linked to the treatment unit, and the tomotherapy approach.

Simple portal imaging approaches that do not use computer assistance are not considered to be suitable for this study.

When the treatment equipment is not equipped with any device that allows direct visualization of anatomical structures using the treatment beam, the recommendations of AAPM Task Group Report 142 for testing the coincidence of the imaging and treatment reference points must be implemented. For example, verification of treatment and imaging isocenter coincidence must be performed routinely for the CyberKnife, Tomotherapy units as well as any BrainLab equipment that does not include an electronic portal imaging device (EPID) that intercepts the treatment beam.

7.1.2.3 Target Volume Definition

Non-Spinal Osseous Sites**:** GTV= gross tumor apparent on CT or MRI, or PET/CT imaging. CTV= GTV. PTV will be uniform expansion of 3 to 5 mm.

Spinal Osseous Sites: GTV= gross tumor apparent on CT or MRI, or PET/CT imaging. The GTV will include 1 of the following:

(a) The vertebral body only **OR**

(b) The vertebral body and pedicle **OR**

(c) Posterior elements only

CTV= GTV. PTV will be as per RTOG 0631.

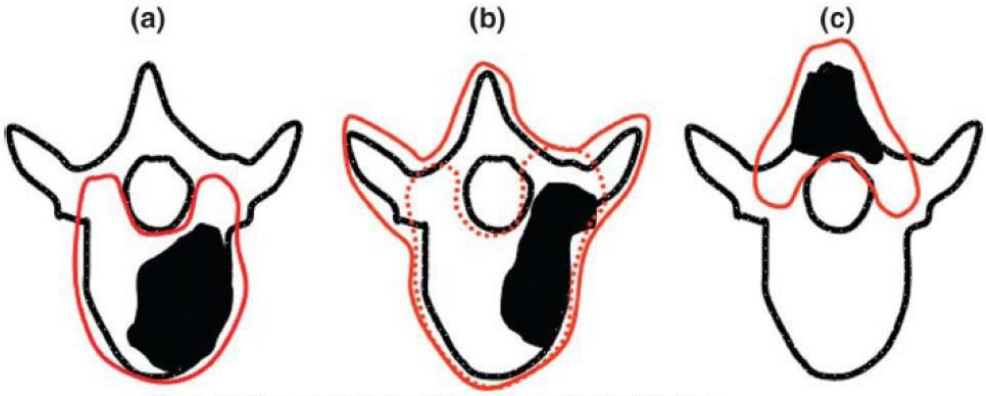

Figure 2: Diagram of Spine Metastasis and Target Volume

7.1.2.4 Planning Techniques

General Considerations: A variety of planning techniques can be used to deliver SBRT for each metastasis. General guidelines include the following:

- Multiple coplanar or non-coplanar beam arrangements are acceptable.
- Typically 7 to 13 static radiation beams with equal weighting are used. It is recommended that at least 10 beams be used when possible.
- A minimum field dimension of 3 cm should be observed treating small metastases.
- Dynamic conformal arcs are acceptable. It is recommended that arcs span at least 340 degrees.
- For non-IMRT or dose painting techniques, the conformal field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3 cm when treating small lesions.
- The prescription isodose line covering 95% the PTV will generally be 80-90% but may range from 60-90% where the maximum dose is 100%. As a result, a "hotspot" will exist within the PTV that is equal to the prescription dose divided by the prescription isodose line (i.e., 45Gy/0.6 = 75Gy when 45Gy is prescribed to the 60% isodose).
- Doses higher than the prescription isodose (i.e., hotspots) should be manipulated to occur within the target.

Dose calculations: All dose distributions shall include corrections for tissue heterogeneities. **Normalization:** The treatment plan should be initially normalized such that 100% corresponds to the maximum dose within the PTV

(MAXPTV). While this point will typically correspond to the PTV center of mass, it can be located elsewhere within the PTV.

1. **Prescription Isodose Surface Coverage**: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface. Doses less than 95% of the prescription dose are restricted to the outside edges of the PTV. The prescription isodose surface selected MUST be ≥ 60% and ≤90% of the dose maximum within the PTV (MAXPTV). The MAXPTV corresponds to the normalization point (100%) of the plan as noted above.
2. **Target Dose Heterogeneity**: Rather than prioritizing target dose homogeneity, SBRT treatment planning prioritizes adequate minimum target coverage and rapid dose fall-off gradients outside of the target. Hot spots within targets are generally accepted without consequence since targets are mostly tumor. The only exception is when the hotspot within the PTV also intersects an OAR.
3. **Critical Organ Doses**: Respect all critical organ dose volume limits as described by either: The report of AAPM Task Group 101, the NRG BR-001 protocol, or the RTOG 0631 treatment protocol.
4. **High-Dose Spillage:**

a. *Location*: Any dose > 105% of the prescription dose should occur within the PTV and not within the normal tissues outside the PTV.

b. *Volume:* Acceptable isodose distributions should be as conformal as possible. To this end the ratio of prescription isodose volume to PTV should be as small as possible.

i. The ratio of the prescription isodose volume to the PTV volume should be < 1.2. Acceptable variations include a ratio of 1.2 to 1.5. Ratios above 1.5 will be considered unacceptable variations. The prescription line for each lesion will be contoured for calculation of this ratio. The prescription line will be labelled as V_5000 with the 5000 changing to reflect the prescription dose in cGy.

ii. Guidelines for the ratio of the 50% prescription isodose volume to the PTV volume (R50%) and for the maximum dose at 2cm (D2cm) from the PTV are given in Table 7.1.2.4. Because it may become more difficult to restrict the 50% isodose volume when dose is summed from treatment of multiple metastases, this ratio should be evaluated for dose calculated for a single metastasis (i.e., not for composite dose). This is acceptable as long as normal tissue constraints are met.

iii. Elliptically shaped metastases as well as extremity metastases may not meet these guidelines. This is acceptable as long as normal tissue constraints are respected.

iv. These criteria will not be required in treating very small tumors (<2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3 cm results in the inability to meet a conformity ratio of 1.5.

Table 7.1.2.4

PTV Volume (cc)	Ratio of 50% Prescription Isodose Volume to PTV Volume, R50%	Maximum Dose at 2cm (D2cm) from PTV in any direction as % of Prescribed Dose
1.8	< 7.5	<57.0
3.8	< 6.5	<57.0
7.4	< 6.0	<58.0
13.2	< 5.8	<58.0
22.0	< 5.5	<63.0
34.0	< 5.3	<68.0
50.0	< 5.0	<77.0
70.0	< 4.8	<86.0
95.0	< 4.4	<89.0
126.0	< 4.0	<91.0
163.0	< 3.7	<94.0

NOTE: For values of PTV dimension or volume not specified, linear interpolation between table entries is required.

NOTE: For tumors within 2 cm of the skin, it may be difficult to meet the values for D2cm and R50%. In these cases, these criteria will not be used.

7.2 **Radium-223**

Radium Ra-223 dichloride will be delivered intravenously at 55 kBq (1.49 mCi)/kg (+/- 10% total dose) for a total of six cycles. 1 cycle= 28 days. The first cycle will commence at study enrollment, then cycles 2 through 6 will commence after the completion of radiotherapies at 4-week intervals.

7.2.1 How Supplied, Stored, Packaged, and Labeled

The alpha-pharmaceutical Radium Ra-223 dichloride is a ready-to-use, sterile, non-pyrogenic, clear, and colorless aqueous solution of Radium Ra-223 dichloride ($^{223}RaCl_2$) for IV administration. It should not be diluted or mixed with any solutions. Each vial is intended for a single use only. Radium-223 ordering documents are located in Appendix 17.3 Clinical Supply Agreement. Instructions for Huntsman Cancer Institute may be performed using the HCI Ordering and Scheduling Process for Radium.

Radium Ra-223 dichloride is an alpha particle emitter with a physical half-life of 11.4 days. The product is isotonic and has a pH of 6.0 to 8.0.
The radioactive concentration at the reference date is 1,100 kBq/mL. The product has a pre-calibration of 14 days. When administered on a day other than the

reference day, the volume should be corrected according to the physical decay table accompanying each shipment.

Decay Correction Factor Table

Days from reference date	Decay Factor	Days from reference date	Decay Factor
-14	2.296	0	0.982
-13	2.161	1	0.925
-12	2.034	2	0.870
-11	1.914	3	0.819
-10	1.802	4	0.771
-9	1.696	5	0.725
-8	1.596	6	0.683
-7	1.502	7	0.643
-6	1.414	8	0.605
-5	1.330	9	0.569
-4	1.252	10	0.536
-3	1.178	11	0.504
-2	1.109	12	0.475
-1	1.044	13	0.447
		14	0.420

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

The volume per vial is 6 mL, corresponding to 6.6 MBq at the reference day. Radium Ra-223 dichloride has a shelf life of 28 days from production day, when stored at ambient temperature. The shelf life has been demonstrated for temperatures from cold storage (2-8°C) up to 40°C. In addition, it has been shown that the product quality is not jeopardized upon freezing.

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

7.2.2 General warning RA-223

Radium-223 dichloride should be received, used, and administered only by authorized persons in designated clinical settings. The receipt, storage, use, transfer, and disposal Radium-223 dichloride are subject to the regulations and/or appropriate licenses of the competent official organization. Radium-223 dichloride should be handled by the user in a manner that satisfies both radiation

safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

7.2.3 Radiation protection RA-223

The administration of Radium Ra-223 dichloride is associated with potential risks for other persons (e.g., medical staff, care givers, and members of the patient's family) from radiation or contamination from spills of body fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations.

For drug handling
Follow the normal working procedures for the handling of radiopharmaceuticals and use universal precautions for handling and administration such as gloves and barrier gowns when handling blood and bodily fluids to avoid contamination. In case of contact with skin or eyes, the affected area should be flushed immediately with water. In the event of spillage of Radium Ra-223 dichloride, the local radiation safety officer should be contacted immediately to initiate the necessary measurements and required procedures to decontaminate the area. A complexing agent such as 0.01 M ethylene-diaminetetraacetic acid (EDTA) solution is recommended to remove contamination.

For patient care
Whenever possible, patients should use a toilet and the toilet should be flushed several times after each use. When handling bodily fluids, simply wearing gloves and hand washing will protect caregivers. Clothing soiled with Radium Ra-223 dichloride or patient fecal matter or urine should be washed promptly and separately from other clothing.

Radium-223 is primarily an alpha emitter, with a 95.3% fraction of energy emitted as alpha-particles. The fraction emitted as beta-particles is 3.6%, and the fraction emitted as gamma-radiation is 1.1%. The external radiation exposure associated with handling of patient doses is considerably lower in comparison to other radiopharmaceuticals for therapeutic purposes as the administered radioactivity will usually be below) (8.8MBq(0.238mCi)). In keeping with the **A**s **L**ow **A**s **R**easonably **A**chievable (ALARA) principle, for minimization of radiation exposure, it is recommended to minimize the time spent in radiation areas, to maximize the distance to radiation sources, and to use adequate shielding. Any unused product or materials used in connection with the preparation or administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations. The gamma radiation associated with the decay of Radium-223 and its daughters allows for the radioactivity measurement of Radium Ra-223 dichloride and the detection of contamination with standard instruments.

Dose calibration

Radium Ra-223 dichloride can be measured in a normal dose calibrator instrument. A vial of Radium Ra-223 dichloride for technical use will be sent to the study center.

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

7.2.4 Dosimetry

The absorbed radiation dose calculation was performed based on clinical biodistribution data. Calculations of absorbed doses were performed using OLINDA/EXM (Organ Level INternal Dose Assessment/EXponential Modeling), a software based on the Medical Internal Radiation Dose (MIRD) algorithm, which is widely used for established beta and gamma emitting radionuclides. For Radium-223, which is primarily an alpha emitter, additional assumptions were made for the intestine, red marrow and bone/osteogenic cells to provide the best possible absorbed dose calculations for Radium Ra-223 dichloride, considering its observed biodistribution and specific characteristics. For an administered activity of 4.00 MBq (0.109 mCi) ((55kBq (.0015 ciper kg body weight to a 73-kg adult), the calculated absorbed doses to the bone (osteogenic cells) is 4.2050 Gy (420.5 rad) and to the red marrow is 0.5066 Gy (50.66 rad). The calculated absorbed doses to the main excretory organs are 0.0265 Gy (2.65 rad) for the small intestine wall, 0.1180 Gy (11.8 rad) for the upper large intestine wall and 0.1696 Gy (16.96 rad) for the lower large intestine wall.
The calculated absorbed doses to other organs are low, e.g. heart wall (0.0063 Gy, 0.63 rad), lung (0.0003 Gy, 0.03 rad), liver (0.0109 Gy, 1.09 rad), kidneys (0.0117 Gy, 1.17 rad), urinary bladder wall (0.0147 Gy, 1.47 rad), testes (0.0003 Gy, 0.03 rad), and spleen (0.0003 Gy, 0.03 rad).

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

7.2.5 Dose handling

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

of Radium Ra-223 dichloride. All administrations of Radium Ra-223 dichloride are based on the certified activity of Radium Ra-223 dichloride at the calibration date.

7.2.6 Dose calculation

The dosage of Radium Ra-223 dichloride is 55 kBq (1.49 mCi)/kg body weight (as documented in the written directive) (+/- 10% total dose). 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.

For example: If the radioactive concentration at the reference date is 11,100 kBq/mL then the volume to be administered for the current dose is calculated as follows:

$$\frac{\text{Body weight (kg)} \textbf{ X } \text{dose (55kBQ/kg body weight)}}{\text{DK factor X 1100kBq (0.0297 μCi)/mL}}$$

7.2.7 Dose preparation

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

7.2.8 Dose administration

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

7.3 **Prohibited Concomitant Medications**

- Concurrent anti-cancer therapy (chemotherapy, androgen deprivation therapy, immunotherapy, biologic therapy, or tumor embolization) other than Ra-223 dichloride and external beam radiation as specified in this protocol.

- Prior use of Radium-223 dichloride.

- Concurrent use of another investigational cytotoxic drug or cytotoxic device therapy (i.e., outside of study treatment) during, or within 4 weeks of trial entry (signing of the informed consent form). However, concomitant use of FDA approved nuclear medicine imaging agents (e.g., Fluciclovine, Choline C-11) used in an investigational imaging context will not be considered a contraindication to enrolling or continuing participation in the study.

- Major surgery within 30 days prior to start of study drug.

7.4 **Duration of Therapy**

Subjects must be withdrawn from the study treatment for the following reasons:

Patients are expected to receive one neo-adjuvant dose of Radium-223 followed by EBRT for 2 to 6 weeks followed by 5 additional cycles of Radium-223. The treatment phase of the study should be completed in approximately 6 months pending dose delay or discontinuation

- Subject withdraws consent from the study treatment and/or 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.
- Disease progression as defined in section 10

- In the event of disease progression, the subject will no longer receive study treatment, but will remain on the study for all follow-up evaluations, which include indicated imaging studies, lab draws, and all questionnaires.

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.

8 TOXICITIES AND DOSEAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for adverse event and serious adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded: (**http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx**).

8.1 Dose Modifications

8.1.1 Dose Modification

Every effort should be made to administer the full dosing regimen of Radium Ra-223 dichloride. Adjustment of dose level is not permitted.
Study visits for administration of Radium-223 during the treatment period should occur at 28 day intervals (within a window of 0 and +14 days). Radium-223 cannot be administered earlier than 28 days from the previous administration. Dosing delays may be instituted under the following circumstances:

Disease progression:
The Investigator should delay cytotoxic chemotherapy, other systemic radioisotope, hemibody external radiotherapy or other investigational drug until the follow-up period. If such treatments have to be given during the treatment period, further study drug administrations must be discontinued.

Patients with a single PSA result that meets biochemical progression criteria may continue on treatment, at the investigator’s discretion, until a confirmatory PSA result is returned. Upon confirmed biochemical progression study treatment MUST be discontinued.

Patients who demonstrate radiographic or clinical progression must discontinue study treatment.

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

• If a patient experiences CTCAE v4.03 Grade 3 or 4 neutropenia, thrombocytopenia, or anemia the administration of study drug should be delayed until recovery to Grade 2 or better.

• If a patient experiences CTCAE v4.03 Grade 3 or 4 neutropenia, thrombocytopenia, or anemia lasting > 14 days, further study drug administrations must be discontinued.

• Blood transfusion is acceptable between study drug administrations but not prior to the start of the study. Use of biologic response modifiers, such as G-CSF or GM-CSF, is allowed in the management of acute toxicity.

• Hematologic evaluation of patients must be performed at baseline and prior to every dose of Radium Ra-223 dichloride. Before the first administration of Radium Ra-223 dichloride, the absolute neutrophil count (ANC) should be $\geq 1.5 \times 10^9$/L, the platelet count $\geq 100 \times 10^9$/L and hemoglobin ≥ 10 g/dL. Before subsequent administrations of Radium Ra-223 dichloride, the ANC should be $\geq 1.0 \times 10^9$/L and the platelet count $\geq 50 \times 10^9$/L and hemoglobin ≥ 9.0 g/dL. If there is no recovery to these values within 6 to 8 weeks after the last administration of Radium Ra-223 dichloride, despite receiving supportive care, further treatment with Radium Ra-223 dichloride should be discontinued. Patients with evidence of compromised bone marrow reserve should be monitored closely and provided with supportive care measures when clinically indicated. Discontinue Radium Ra-223 dichloride in patients who experience life-threatening complications despite supportive care for bone marrow failure.

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

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

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

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

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

Any Other Toxicity:
Local practice will apply.

8.2 Supportive Care

8.2.1 All supportive measures consistent with optimal patient care will be given throughout the study.

9 STUDY CALENDAR

1 cycle = 28 days[11]

Examination	**Screening[1]**	**Neo-adjuvant C1**	**EBRT**	**C2[7]**	**C3**	**C4**	**C5**	**C6**	**End of Treatment[17]**	**Follow-up[8]**
Informed consent	**X**									
Medical history	**X**									
Eligibility criteria	**X**									
Vital signs	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	
Physical examination[18]	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Karnofsky Performance Status or ECOG Equivalent (Appendix 17.5)[18]	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	
Concomitant Medications[18]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Events[14]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Hematology[2, 13]	**X**	**X[13]**		**X[13]**	**X[13]**	**X[13]**	**X[13]**	**X[13]**	**X**	
Chemistry[3, 13]	**X**	**X[13]**		**X[13]**	**X[13]**	**X[13]**	**X[13]**	**X[13]**	**X**	
ECG[5]	**X**									
CT or MRI[4]	**X**								**X**	
Radium-223[16]		**X**		**X**	**X**	**X**	**X**	**X**		
EBRT			**X**							
PSA and Testosterone[9, 13]	**X**	**X**	**X[9]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Bone scans[6]	**X**			**X[12]**	**X[12]**	**X**	**X[12]**	**X[12]**	**X**	**X**
QOL questionnaires	**X**		**X[15]**			**X**			**X**	**X**
Myriad CCP[10]	**X**									
Myriad HRD[10]	**X**									

1 ALL Pre-study/Screening procedures should be completed within 4 weeks of study enrollment - with the exception of laboratory tests which need to be completed within 2 weeks prior to study enrollment, and imaging assessments which must be completed within 90 days of enrollment. Consent may be signed ≤ 45 days prior to cycle one day one.
2 Hematology includes CBC with differential and platelets.
3 Chemistry includes Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, Urea Nitrogen. 4 CT-based scans (either Fluciclovine PET/CT or diagnostic CT) or MRI that includes the chest, abdomen and pelvis. A similar imaging modality (MRI or CT-based) used at screening is preferred, but not required at follow up evaluation. Diagnostic CT at follow-up is sufficient if PET/CT was used at screening. Disease assessment to be conducted by PCWG2 and RECIST 1.1 section 10.1.1.
5 ECG will be done only if medically indicated.
6 Bone scans should be obtained between cycle 3 and 4 of the study dependent on any dose delays that may extend cycle time. Bone scans should be performed 2-4 weeks after the final Radium-223 dose. Bone scans will also be performed at any sign of progression as defined in section 10.
7 Cycle 2 may be delivered concurrently with external beam radiation to the primary site. Therefore, cycle 2 will NOT be delayed to allow completion of the external beam radiation.
8 Follow-up visits will occur every 3 months (+90/-30 days) for an approximate duration of two years from the time patients are enrolled on the study.
9 PSA and Testosterone within 24 hours prior to or after starting external beam radiation.
10 Correlative studies are OPTIONAL; refer to section 14.1 for archival tissue instruction
11 Cycles should occur at least 28 days after the previous cycle and no more than 42 days after the previous cycle (0 to +14 days).
12 Bone scans are optional at the time points indicated by this superscript and will be performed if there is clinical suspicion of progression that falls outside the objective criteria of progression for this study.
13 All post-screening laboratory tests should be drawn approximately 7 days, but no fewer than 3 business days, before radium dosing. Laboratory tests for CBC differential platelets must have results available prior to radium ordering. Laboratory safety assessments MUST be performed and resulted prior to radium dosing.
14 The collection of all adverse events will begin after the first dose of study treatment and end 30 days after the last dose of study treatment. The collection of treatment related adverse events will continue until the last study visit (or until new cancer treatment is initiated, if sooner).
15 QOL Questionnaires should be completed on the final day of EBRT ± 7days.
16 If a patient meets biochemical progression, the patient may continue to receive treatment, at the Investigator's discretion, until a validated PSA test has confirmed biochemical progression.
17 End of treatment visit will occur 28 days (±7 days) after last treatment is administered.
18 Physical exam, KPS or ECOG equivalent, and concomitant medications do not need to be repeated if they have been performed less than 7 days prior.

10 CRITERIA FOR EVALUATION AND ENDPOINT

Assessment of clinical outcomes:

Clinical outcomes will be assessed at various time points from the start of protocol treatment. Patients will be followed for a total of 2 years after enrollment.
A study subject that completes Cycle 1 of Tadium-223, EBRT, and at least 3 cycles of Radium-223 will be considered evaluable.

10.1 Primary Endpoint – 15 month Hormone Free Survival

The primary objective is to determine the hormone-therapy-free survival time for men treated with sequential EBRT and Radium-223 and determine whether it is a 20% risk reduction over the institutional comparator of 100% use of systemic therapy by 15 months. The primary outcome is 15 months hormone-free survival. Patients will remain on study treatment for the duration defined by the calendar or for disease progression. Patients will be followed up to determine the start of ADT which will be used to measure the primary end point.

For the purposes of this study, progression will be measured after the completion of EBRT and the delivery of Cycle 2 of Radium-223 and defined as either:

Biochemical Progression:

- For those subjects whose PSA is greater than 20ng/ml at baseline who do not have any PSA decrease after starting therapy: biochemical progression will be defined as a 10% rise over the baseline.

- For those subjects whose PSA is greater than 20ng/ml at baseline, who demonstrate decrease in PSA after study treatment: if the PSA nadir remains > 20ng/ml, biochemical progression will be defined as a PSA rise greater than 10% of the PSA nadir. If the PSA nadir is < 20ng/ml, biochemical progression will be defined as a PSA rise greater than 10% of the PSA nadir.

-For those subjects whose PSA is less than 20ng/ml at baseline: biochemical progression will be defined as PSA >20ng/ml and 10%.

*Any PSA test that would meet a failure definition has to be validated through Huntsman Cancer Institute or a Veterans Affairs Hospital with a repeat PSA test no sooner than 5 days and no later than 14 days from the initial notification of the result demonstrating progression.

OR

Radiographic progression: Any new, progressing, or reappearing lesion on Bone Scan, CT/Scan, or MRI compared to the same scan performed previously. Radiographic Progression will be determined by Prostate Cancer Clinical Trials Working Group (PCWG2) and RECIST 1.1 as described below (section 10.1.1).

* Of note: For a patient to meet radiographic progression criterion for appearance of new bone lesion only, the patient must demonstrate appearance of new bone disease, as confirmed by the treating radiation oncologist, and also meet the biochemical progression definition set out above.

OR

Clinical Progression: the development of any skeletal related event defined as: time to any EBRT not required as a study procedure, time to first pathological bone fracture, time to spinal cord compression, or time to surgical intervention.

RECIST 1.1 and PCGW 2 Assessments:

The following definitions and criteria for RECIST 1.1 and PCWG2 should be used for the baseline evaluations of existing disease and for the ongoing evaluation of tumor responses.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter (LD) ≥ 10 mm using CT, MRI, or caliper measurements or ≥20 mm with x-ray.
Non-measurable lesions - all other lesions including small lesions (LD < 10 mm with CT, MRI, or caliper measurements or <20 mm with x-ray).

Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinical assessments).
- A sum of the LD for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

RECIST Response Criteria

	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions (Must persist for a minimum of four weeks)
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD (Must persist for a minimum of four weeks)
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

	Evaluation of non-target lesions
Complete Response (CR)	Disappearance of all non-target lesions
Stable Disease (SD)	Persistence of one or more non-target lesion(s)
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

RECIST Evaluation of Overall Response

The best overall response is the best response observed until progression/recurrence and is determined as indicated in the table below:

Target Lesions	**Non-Target Lesions**	**Evaluation of New Lesions**	**Overall Response**
CR	CR	No	CR
CR	SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Radionuclide Bone Scan Assessment

Bone scan lesions should be enumerated at baseline. Questionable lesions, e.g., sites of previous fracture, may require confirmation by CT or MRI.

Post-baseline Assessments and Definition of Progression of Bone Metastases

Disease Based on Radionuclide Bone Scan

Bone scan lesions should be assessed and enumerated at each follow-up assessment.

Progression on bone scan is defined as 2 or more new lesions on radionuclide bone scans. Should 2 or more new bone lesions be evident at the first assessment on treatment (end of cycle 3), 2 or more additional new lesions must be evident on a confirmatory assessment at least 6 weeks later (and no sooner than end of cycle 6). This confirmation is not required when 2 or more new lesions (compared to baseline or to the end of cycle 3 assessment) first appear after the first follow-up assessment, i.e., at end of cycle 6 or thereafter.

Should new bone lesions be documented at end of cycle 3 but not confirmed at end of cycle 6, then end of cycle 3 scan becomes the new baseline and 2 or more new lesions at subsequent assessments relative to end of cycle 3 defines bone scan progression.

Stable disease (SD) on bone scan stable disease is defined as the absence of progression. Bone scan lesions are considered non-evaluable under RECIST, and thus there can be no partial response. Complete response is very rare. Thus, almost all bone scans will be rated as NE (no lesions present), SD, or PD.

Overall Response Assessment

The following table summarizes the overall response status calculation at each time point for patients who have either RECIST 1.1 evaluable soft tissue lesions and/or radionuclide bone scan lesions. Note that CR can only occur if there are RECIST 1.1-evaluable lesions and no bone lesions based on radionuclide bone scan. PR can occur if patients have CR or PR based on soft tissue evaluation and bone scan lesions that are stable.

Overall Assessment Time Point Response

PCWG2 Target/Nontarget soft tissue/RECIST 1.1	Bone Scan (PCWG2)	Overall
CR	No Metastases (NE)	CR
CR,PR	SD	PR
SD	SD	SD
PD	SD	PD
SD	PD	PD

10.2 Myriad CCP Correlative studies.

These studies are already FDA-approved, standard-of-care studies, and will not be required for participation on this clinical trial. For those patients consenting to these

correlative studies, existing banked biopsy tissues from the original prostate specimens will be used for the Myriad CCP testing. Procedures for testing these tissues will be per existing clinical protocols.

10.3 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner).

Vital Signs

Vital signs include blood pressure, respiratory rate, pulse rate and temperature.

Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the Study Calendar.

10.4 Stopping Rules

10.4.1 Toxicity: If 6 of the first 8 treated subjects develop 2 or more CTCAE grade 3 toxicities related to study drug, it will be reviewed by the DSMC to determine if the trial will continue.

11 STATISTICAL CONSIDERATIONS

The primary objective is to determine the hormone-therapy-free survival time for men treated with concurrent EBRT and Radium-223 and determine whether 20% of subjects do not meet the progression endpoint and require ADT at 15 months. The primary outcome is 15 months hormone- (or other systemic) therapy-free survival. The null hypothesis is that 99% of subjects will start systemic therapy within 15 months. The alternative hypothesis is that 80% of subjects will start systemic therapy within 15 months. With 20 evaluable subjects there will be 93% power for this alternative hypothesis using an exact binomial test at the one-sided 0.05 significance level. The null hypothesis will be rejected if 2 or more out of 20 subjects are not placed on systemic therapy within one year.

One of the secondary endpoints is to determine the hormone-therapy-free survival time for men treated with concurrent EBRT and Radium-223 and determine whether it is a 30% risk reduction over the SWOG intermittent ADT historic cohort. This secondary hypothesis will be tested only if the primary null hypothesis is rejected. The outcome for

this secondary hypothesis is 15 month hormone- (or other systemic) therapy-free survival. In 2012 a SWOG cooperative group trial reported that 78% of subjects on intermittent androgen therapy had resumed ADT within 15 months, and this proportion will be used as a null hypothesis. With 20 evaluable subjects, and a null hypothesis that 78% or more of patients will start systemic therapy within 15 months there will be 80% power to detect an alternative hypothesis that 48% or fewer will start systemic therapy within 15 month using an exact binomial test at one-sided alpha =0.05 significance level.

Additional, secondary endpoints are time to first skeletal related event (SRE), overall survival, PSA doubling time, overall survival and toxicities. All secondary endpoints will be evaluated descriptively. Time to first SRE, OS, and PSA doubling time will be analyzed via Kaplan-Meier product limit methods and associated 95% confidence intervals. Toxicities will be tabulated using CTAE version 4.0. The number and proportion of subjects with toxicities will be reported.

Exploratory endpoints are to evaluate if a commercially available cell-cycle progression gene assay (Myriad CCP) performed on the original prostate biopsy or surgical pathology specimen correlates with biochemical or clinical progression free survival in the study population.

Correlations with survival endpoints will be performed using exploratory Cox proportional hazards regression analysis.

Primary analysis and report planned at 15 months of follow up for all enrollees.

Health-related Quality of Life as scored by EPIC urinary, bowel, sexual, and hormonal domains, as well as PROMIS-29 questionnaires.

Medians, ranges, and quartiles will be computed for all health-related Quality of Life domains. Exploratory logrank tests will be used to relate domain scores to survival outcomes (hormone-free survival, time to first skeletal event, overall survival, and PSA doubling time).

12 REGISTRATION GUIDELINES

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.

Study-related screening procedures can only begin once the patient has signed a consent form. Patients must not begin protocol treatment prior to registration.

Treatment should start within 21 working days after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to: CTORegistrations@hci.utah.edu.

13 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRFs should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. **Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.** These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility, and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

14 SPECIAL INSTRUCTIONS

14.1 Myriad CCP and HRD Analysis

Either prostate biopsy tissue or radical prostatectomy specimens previously collected at the time of diagnosis and/or surgery will be used for the Myriad CCP and HRD assay. There will not be additional tissue collections for this clinical study. Samples from the respective pathology departments will be submitted to Myriad in accordance with the specimen handling requirements of the commercially available test.

Details about CCP can be found at: https://prolaris.com/prolaris-for-physicians/for-pathologists/sample-requirements/

Details about HRD can be found at: https://mychoicehrd.com/physicians/

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB-approved version.

15.2 Institutional Review

Study will be approved by the Institutional Review Board of University of Utah.

15.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) and approved by the NCI to assure the well-being of patients enrolled on Investigator-Initiated Trials that do not have an outside monitoring review. Roles and responsibilities of the DSMC are set forth in the NCI-approved plan. The activities of this committee include a quarterly review of adverse events including SAEs, important medical events, significant revisions or amendments to the protocol, and approval of cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

All **phase II** studies are reviewed by the full committee at each quarterly DSMC meeting. This includes a review of all serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates as well as all grade 3 or greater toxicities for patients on treatment and within 30-day follow-up window (only if possibly, probably, or definitely related).

15.4 Adverse Events / Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for AE and SAE reporting. An electronic copy of the CTCAE Version 4.0 can be downloaded from:
http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx

15.4.1 Adverse Events (AE)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug, even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The collection of all adverse events will begin after the first dose of study treatment and end 30 days after the last dose of study treatment. The collection of treatment-related adverse events will continue until the last study visit (or until new cancer treatment is initiated, if sooner),

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, discovered by clinical research coordinator interview, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade based on CTCAE v.4 (grade 1-5)
2. its relationship to Radium-223 or EBRT (definite, probable, possible, unlikely, not related).
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see section 8 for guidance). Once an adverse event is detected, it should be followed until its resolution or if patient's participation on the study is terminated or otherwise discontinued, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about Radium-223 is described in the Drug Information (section 3) and the most recent Investigator Brochure. This

information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

15.4.2 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded in compliance with all institutional and government requirements. A serious adverse event is an undesirable sign, symptom, or medical condition that:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- causes congenital anomaly or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition

The collection of serious adverse events will begin after the first dose of study treatment and end 30 days after the last dose of study treatment. The collection of treatment-related serious adverse events will continue until the last study visit (or until new cancer treatment is initiated, if sooner).

Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended, but which is felt to be treatment related, must be reported.

Toxicities that fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above must simply be documented as AEs in the patient research chart.

15.5 SAE Reporting Requirements

SAEs must be reported to the DSMC, the FDA, the IRB, and Bayer according to the requirements described below:

A MedWatch 3500A form must be completed and submitted to compliance@hci.utah.edu within 1 business day of first knowledge or notification of the event.

DSMC Notifications:

- An HCI Research Compliance Officer (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for each individual study.
- The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the quarterly DSMC meeting.

FDA Notifications:

- Adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:
    - Serious
    - Unexpected
    - Definitely, Probably, or Possibly Related to the investigational drug
    - Fatal or life-threatening events that meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator, followed by as complete a report as possible within 8 additional calendar days.
- All other events that meet the criteria above will be reported within 15 calendar days after first knowledge of the event by the investigator.
- The RCO will review the MedWatch report for completeness, accuracy, and applicability to the regulatory reporting requirements.
- The RCO will ensure the complete, accurate, and timely reporting of the event to the FDA.
- The Regulatory Coordinator will submit the report as an amendment to the IND application.
- All other adverse events and safety information not requiring expedited reporting that occur or are collected during the course of the study will be summarized and reported to the FDA through the IND Annual Report.

IRB Notification:

- Events meeting the University of Utah IRB reporting requirements (http://www.research.utah.edu/irb/) will be submitted through the IRB's electronic reporting system within 10 working days.

Bayer Notifications:

An ADEERS form (Adverse Event Expedited Reporting System) available at
http://ctep.cancer.gov/reporting/adeers.html
OR
A MedWatch form
All reports shall be sent electronically to:

Electronic Mailbox:	DrugSafety.GPV.US@bayer.com
Facsimile:	(973) 709-2185
Address: **Mail only:**	Global Pharmacovigilance - USA Bayer HealthCare P.O. Box 915Whippany, NJ 07981-0915
Address: **FDX or UPS only**	100 Bayer Blvd., Whippany, NJ 07981 67 Whippany Road, Whippany, NJ 07981 for UPS

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

Phone:	1-888-842-2937

*Medwatch 3500A form can be found at
http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/ucm082728.pdf

15.6 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject, including the pregnancy of a male subject's female partner as an SAE. Pregnancies or lactation that occurs during the course of the trial or with 30 days of completing the trial or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC, IRB, FDA, and the sponsor as applicable. All subjects and female partners who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events.

15.7 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

Any amendments to the protocol that significantly affect the safety of subjects, scope of the investigation, or the scientific quality of the study are required to submit the amendment for FDA review.

15.8 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

15.9 FDA Annual Reporting

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect. (21 CFR 312.33).

15.10 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

15.11 Record Keeping

Per 21 CFR 312.57, Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

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17 APPENDIX

17.1 PROMIS-29 Questionnaire

RROPE

PROMIS-29 Questionnaire

Patient Study ID: 102312-01-____ ____ ____

Patient Initials: ____ ____ ____

Date of Completion: ____ / ____ / _____

PROMIS–29 Profile v1.0

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
1	Are you able to do chores such as vacuuming or yard work?	☐	☐	☐	☐	☐
2	Are you able to go up and down stairs at a normal pace?	☐	☐	☐	☐	☐
3	Are you able to go for a walk of at least 15 minutes?	☐	☐	☐	☐	☐
4	Are you able to run errands and shop?	☐	☐	☐	☐	☐
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
5	I felt fearful	☐	☐	☐	☐	☐
6	I found it hard to focus on anything other than my anxiety	☐	☐	☐	☐	☐
7	My worries overwhelmed me	☐	☐	☐	☐	☐
8	I felt uneasy	☐	☐	☐	☐	☐
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
9	I felt worthless	☐	☐	☐	☐	☐
10	I felt helpless	☐	☐	☐	☐	☐
11	I felt depressed	☐	☐	☐	☐	☐
12	I felt hopeless	☐	☐	☐	☐	☐
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
13	I feel fatigued	☐	☐	☐	☐	☐
14	I have trouble starting things because I am tired	☐	☐	☐	☐	☐
	In the past 7 days…					
15	How run-down did you feel on average?	☐	☐	☐	☐	☐
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
16	How fatigued were you on average?	☐	☐	☐	☐	☐

PROMIS–29 Profile v1.0

	Sleep Disturbance **In the past 7 days…**	Very poor	Poor	Fair	Good	Very good
17	My sleep quality was.....	☐	☐	☐	☐	☐
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
18	My sleep was refreshing.....	☐	☐	☐	☐	☐
19	I had a problem with my sleep	☐	☐	☐	☐	☐
20	I had difficulty falling asleep	☐	☐	☐	☐	☐
	Satisfaction with Social Role **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
21	I am satisfied with how much work I can do (include work at home)	☐	☐	☐	☐	☐
22	I am satisfied with my ability to work (include work at home).....	☐	☐	☐	☐	☐
23	I am satisfied with my ability to do regular personal and household responsibilities	☐	☐	☐	☐	☐
24	I am satisfied with my ability to perform my daily routines.....	☐	☐	☐	☐	☐
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
25	How much did pain interfere with your day to day activities?.....	☐	☐	☐	☐	☐
26	How much did pain interfere with work around the home?	☐	☐	☐	☐	☐
27	How much did pain interfere with your ability to participate in social activities?	☐	☐	☐	☐	☐
28	How much did pain interfere with your household chores?	☐	☐	☐	☐	☐

Pain Intensity
In the past 7 days…

29	How would you rate your pain on average?.....	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst imaginable pain

Appendix 17.2 EPIC Questionnaire

EPIC

The Expanded Prostate Cancer Index Composite

This questionnaire is designed to measure Quality of Life issues in patients with Prostate cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

Remember, as with all medical records, information contained within this survey will remain strictly confidential.

Today's Date (please enter date when survey completed): Month_____Day_____Year_____

Name (optional): _____

Date of Birth (optional): Month_____Day_____Year_____

Do Not Mark in This Space

1. In general, would you say your health is:

Excellent..... 1
Very good..... 2
Good..... 3 (Circle one number) 11/
Fair..... 4
Poor..... 5

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(Circle 1, 2, or 3 on each line)

	Yes Limited A Lot	Yes, Limited A Little	No, Not Limited At All	
a. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.....	1	2	3	12/
b. Climbing **several** flights of stairs.....	1	2	3	13/

3. During the **PAST 4 WEEKS**, have you had any of the following problems with your work or other regular daily activities as a result of your **PHYSICAL HEALTH**?

(Please answer YES or NO for each question by circling 1 or 2 on each line.)

	Yes	No	
a. **Accomplished less** than you would like	1	2	14/
b. Were limited in the **kind** of work or other activities	1	2	15/

4. During the **PAST 4 WEEKS**, have you had any of the following problems with your work or other regular daily activities as a result of any **EMOTIONAL PROBLEMS**, such as feeling depressed or anxious?

(Please answer YES or NO for each question by circling 1 or 2 on each line)

	Yes	No	
a. **Accomplished less** than you would like	1	2	16/
b. Didn't do work or other activities as **carefully** as usual	1	2	17/

EPIC 2.2002

Do Not Mark in This Space

5. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all 1
Slightly 2
Moderately ..... 3 (Circle one number) 18/
Quite a bit 4
Extremely 5

6. These questions are about how you feel and how things have been with you during the PAST 4 WEEKS. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

(Circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time	
a. Have you felt calm and peaceful?.....	1	2	3	4	5	6	19/
b. Did you have a lot of energy?	1	2	3	4	5	6	20/
c Have you felt downhearted and blue?	1	2	3	4	5	6	21/

7. During the **past 4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time 1
Most of the time.....2
Some of the time.....3 (Circle one number) 22/
A little of the time..... 4
None of the time.....5

EPIC 2.2002

Do Not Mark in This Space

URINARY FUNCTION

This section is about your urinary habits. Please consider **ONLY THE LAST 4 WEEKS**.

8. Over the **past 4 weeks**, how often have you leaked urine?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 23/
About once a week.....4
Rarely or never..... 5

9. Over the **past 4 weeks**, how often have you urinated blood?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 24/
About once a week.....4
Rarely or never..... 5

10. Over the **past 4 weeks**, how often have you had pain or burning with urination?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 25/
About once a week.....4
Rarely or never..... 5

11. Which of the following best describes your urinary control **during the last 4 weeks**?

No urinary control whatsoever.....1
Frequent dribbling..... 2 (Circle one number) 26/
Occasional dribbling..... 3
Total control..... 4

Do Not Mark in This Space

12. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks?**

None	0		
1 pad per day	1		
2 pads per day	2	(Circle one number)	
3 or more pads per day	3		27/

13. How big a problem, if any, has each of the following been for you **during the last 4 weeks?**

(Circle one number on each line)

		No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a.	Dripping or leaking urine	0	1	2	3	4	28/
b.	Pain or burning on urination	0	1	2	3	4	29/
c.	Bleeding with urination	0	1	2	3	4	30/
d.	Weak urine stream or incomplete emptying	0	1	2	3	4	31/
e.	Waking up to urinate	0	1	2	3	4	32/
f.	Need to urinate frequently during the day	0	1	2	3	4	33/

14. Overall, how big a problem has your urinary function been for you **during the last 4 weeks?**

No problem	1		
Very small problem	2		
Small problem	3	(Circle one number)	34/
Moderate problem	4		
Big problem	5		

EPIC 2.2002

Do Not Mark in This Space

Urinary Symptoms
(Circle one number on each line)

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	
15. **Incomplete emptying** Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	35/
16. **Frequency** Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	36/
17. **Intermittency** Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	37/
18. **Urgency** Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	38/
19. **Weak Stream** Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	39/
20. **Straining** Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	40/
21. **Nocturia** Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	**(none)** 0	**(1 x)** 1	**(2 x)** 2	**(3 x)** 3	**(4 x)** 4	**(5x or more)** 5	41/

EPIC 2.2002

Do Not Mark in This Space

BOWEL HABITS

The next section is about your bowel habits and abdominal pain.
Please consider **ONLY THE LAST 4 WEEKS**.

22. How often have you had rectal urgency (felt like I had to pass stool, but did not) **during the last 4 weeks**?

More than once a day	1	
About once a day	2	
More than once a week	3	(Circle one number)
About once a week	4	
Rarely or never	5	

42/

23. How often have you had uncontrolled leakage of stool or feces?

More than once a day	1	
About once a day	2	
More than once a week	3	(Circle one number)
About once a week	4	
Rarely or never	5	

43/

24. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) **during the last 4 weeks**?

Never	1	
Rarely	2	
About half the time	3	(Circle one number)
Usually	4	
Always	5	

44/

25. How often have you had bloody stools **during the last 4 weeks**?

Never	1	
Rarely	2	
About half the time	3	(Circle one number)
Usually	4	
Always	5	

45/

Do Not Mark in This Space

26. How often have your bowel movements been painful **during the last 4 weeks**?

Never	1		
Rarely	2		
About half the time	3	(Circle one number)	46/
Usually	4		
Always	5		

27. How many bowel movements have you had on a typical day **during the last 4 weeks**?

Two or less	1		
Three to four	2	(Circle one number)	47/
Five or more	3		

28. How often have you had crampy pain in your abdomen, pelvis or rectum **during the last 4 weeks**?

More than once a day	1		
About once a day	2		
More than once a week	3	(Circle one number)	48/
About once a week	4		
Rarely or never	5		

29. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Urgency to have a bowel movement	0	1	2	3	4	49/
b. Increased frequency of bowel movements	0	1	2	3	4	50/
c. Watery bowel movements	0	1	2	3	4	51/
d. Losing control of your stools	0	1	2	3	4	52/
e. Bloody stools	0	1	2	3	4	53/
f. Abdominal/ Pelvic/Rectal pain	0	1	2	3	4	54/

30. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem	1		
Very small problem	2		
Small problem	3	(Circle one number)	55/
Moderate problem	4		
Big problem	5		

EPIC 2.2002

Do Not Mark in This Space

SEXUAL FUNCTION

The next section is about your **current** sexual function and sexual satisfaction. Many of the questions are very personal, but they will help us understand the important issues that you face every day. Remember, THIS SURVEY INFORMATION IS COMPLETELY CONFIDENTIAL. Please answer honestly about **THE LAST 4 WEEKS ONLY**.

31. How would you rate each of the following during the last 4 weeks? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good	
a. Your level of sexual desire?	1	2	3	4	5	56/
b. Your ability to have an erection?	1	2	3	4	5	57/
c. Your ability to reach orgasm (climax)?	1	2	3	4	5	58/

32. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?

None at all 1
Not firm enough for any sexual activity 2
Firm enough for masturbation and foreplay only ..... 3 (Circle one number) 59/
Firm enough for intercourse 4

33. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?

I NEVER had an erection when I wanted one 1
I had an erection LESS THAN HALF the time I wanted one 2
I had an erection ABOUT HALF the time I wanted one ..... 3 (Circle one number) 60/
I had an erection MORE THAN HALF the time I wanted one 4
I had an erection WHENEVER I wanted one 5

34. How often have you awakened in the morning or night with an erection **during the last 4 weeks**?

Never 1
Less than once a week 2
About once a week ..... 3 (Circle one number) 61/
Several times a week 4
Daily 5

Do Not Mark in This Space

35. **During the last 4 weeks**, how often did you have <u>any</u> sexual activity?

Not at all	1		
Less than once a week	2		
About once a week	3	(Circle one number)	62/
Several times a week	4		
Daily	5		

36. **During the last 4 weeks**, how often did you have sexual intercourse?

Not at all	1		
Less than once a week	2		
About once a week	3	(Circle one number)	63/
Several times a week	4		
Daily	5		

37. Overall, how would you rate your ability to function sexually **during the last 4 weeks**?

Very poor	1		
Poor	2		
Fair	3	(Circle one number)	64/
Good	4		
Very good	5		

38. How big a problem **during the last 4 weeks**, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Your level of sexual desire	0	1	2	3	4	65/
b. Your ability to have an erection	0	1	2	3	4	66/
c. Your ability to reach an orgasm	0	1	2	3	4	67/

39. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?

No problem	1		
Very small problem	2		
Small problem	3	(Circle one number)	68/
Moderate problem	4		
Big problem	5		

EPIC 2.2002

Do Not Mark in This Space

HORMONAL FUNCTION

The next section is about your hormonal function. Please consider **ONLY THE LAST 4 WEEKS**.

40. **Over the last 4 weeks,** how often have you experienced hot flashes?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 69/
About once a week..... 4
Rarely or never..... 5

41. How often have you had breast tenderness **during the last 4 weeks**?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 70/
About once a week..... 4
Rarely or never..... 5

42. **During the last 4 weeks,** how often have you felt depressed?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 71/
About once a week..... 4
Rarely or never..... 5

43. **During the last 4 weeks,** how often have you felt a lack of energy?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 72/
About once a week..... 4
Rarely or never..... 5

44. How much change in your weight have you experienced **during the last 4 weeks**, if any?

Gained 10 pounds or more.....1
Gained less than 10 pounds 2
No change in weight..... .....3 (Circle one number) 73/
Lost less than 10 pounds 4
Lost 10 pounds or more.....5

EPIC 2.2002

Do Not Mark in This Space

45. How big a problem **during the last 4 weeks**, if any, has each of the following been for you?
(Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Hot flashes.....	0	1	2	3	4	74/
b. Breast tenderness/enlargement..	0	1	2	3	4	75/
c. Loss of Body Hair.....	0	1	2	3	4	76/
d. Feeling depressed.....	0	1	2	3	4	77/
e. Lack of energy.....	0	1	2	3	4	78/
f. Change in body weight	0	1	2	3	4	79/

Overall Satisfaction

46. Overall, how satisfied are you with the treatment you received for your prostate cancer?

Extremely dissatisfied..... 1
Dissatisfied..... 2
Uncertain..... 3 (Circle one number) 80/
Satisfied..... 4
Extremely satisfied..... 5

THANK YOU VERY MUCH!!

Appendix 17.3 Bayer Radium Ordering

Appendix 2

CLINICAL SUPPLY AGREEMENT

Product:	Radium Ra 223 dichloride (BAY88-8223)
Additional information:	Preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State. Follow procedures for proper handling and disposal of radioactive pharmaceuticals.
Primary packaging material:	Xofigo (radium Ra 223 dichloride injection) is available in a glass vial, ready-to-use. The volume per vial is 6 mL, corresponding to 6.6 MBq at the reference day.
Storage instruction for primary packed product:	The product does not require any special temperature storage conditions, and can be stored at ambient temperature. The investigational medicinal product should be stored in accordance with national regulations for radioactive materials.
Each patient dose shall be ordered by the SPONSOR from Cardinal Health at least 3 business days prior to the time of drug administration so that the patient's weight can be transmitted to the Pharmacy for calculating the volume of drug to be disbursed. Unused Clinical Trial Supplies should not be returned to BAYER. The SPONSOR will destruct after completion of the Trial and will document the destruction in the Trial File and the Unused Study Drug Disposition Form attached as Appendix 3.	
Recipient Address (Pharmacy/contact at SPONSOR site):	Intermountain Radiopharmacy Attention: Colin Kelly Crebs 391 Chipeta Way, Suite A Salt Lake City, Utach 84108-1263 Phone: 801-581-8189 Fax: 801-585-7273 Email: kelly.crebs@utah.edu

The order should be placed by faxing the Shipment Request Form that follows to Cardinal Health

Shipment Request Confirmation Fax Form
ISS/IIR
Send to Cardinal Health Denver (Xofigo Pharmacy)
Pharmacy Fax Number: 720-374-7384
Phone: 720-374-4836

ISS/IIR Study Number: IIR-US-

Hospital or Clinic Name:

PI Name:

Shipping Contact Name and telephone number:

Shipping Address:

Rx

_____ _____ _____
Patient's First and Last Name | Patient ID | Patient weight in kg

_____ _____ _____
Treatment date | Treatment time | Time zone

Dose Calculation:
❑ (kg) x 1.49uCi/kg = uCi (total dose)

	Radionuclide	Chemical Form	Dosage Form	Dose Requested (microcuries)	Route of Administration
✓	Ra-223 (Xofigo®)	Dichloride	IV solution	_____ uCi	IV

_____ _____
Printed Physician on RML | Signature Physician on RML

Person Placing Order:_____
(full name)

Date ordered:_____

Order confirmed by: _____
(Pharmacist initials)

Please note that the dose indicated in this order form corresponds to the revised standard reference values for Xofigo as per the United States (US) National Institute of Standards and Technology (NIST) standardization update (agreed on 17 MAR 2015).

Appendix 3

Unused Drug Disposition Form

PRINCIPAL INVESTIGATOR:
BAYER STUDY Number:
Title:

Unused Study Drug Disposition Form
Destruction or Return Confirmation

STUDY DRUG Provided	STUDY DRUG Unused	STUDY DRUG Destroyed	STUDY DRUG Returned

I hereby confirm that the product described above was destroyed or returned (select one) to BAYER on (date) _____at
(address)_____.

Witness (Pharmacist or PI): _____
(Print Name)

Witness: _____
Signature

Telephone Number: _____

Fax Number: _____

E-Mail: _____

Please return this form to (VP of Medical Affairs named in contract) at BAYER HEALTHCARE PHARMACEUTICALS INC., 100 BAYER Blvd., P.O. Box 915, Whippany, NJ 07981-0915

Appendix 17.4 Radium-223 Patient Handouts

Radium Ra 223 dichloride (Xofigo®)

- This is an injection of the radioactive material radium 223, and will be administered in the Nuclear Medicine Department at the Huntsman.
- **Radium 223 (Xofigo®)** is given as an injection into a vein every 28 days for 6 planned doses. Your blood counts must be checked a few days prior to each dose to ensure the next dose is safe to give.
- It is used to treat prostate cancer that is not responding to treatments that lower your testosterone and has spread to your bones.
- It is very important for you to stay hydrated while receiving this medication. Contact the clinic if you are experiencing dehydration, decreased urine output, or decreased ability to drink fluids.
- Most common side effects include:
    - Nausea
    - Diarrhea
    - Vomiting
    - Swelling of the arms or legs (peripheral edema)
    - Low blood cell counts (including your infection fighting cells, hemoglobin, and platelets)
- There are medications that may be prescribed to treat some of the side effects of radium 223. If you experience any intolerable side effects, please contact the Radiation Oncology Front Desk at (801) 581-2396 and ask to speak to a nurse. You can also call the Nuclear Medicine Clinic at (801) 581-2370 or your study coordinator. If it is an emergency please dial 911.
- Follow good hygiene practices to prevent infections. Notify the clinic if you experience bleeding or signs of an infection. Examples of infection include a fever of 100.5°F or higher, chills, or cough.
- Use caution to keep body fluids from coming into contact with family members and caregivers for at least one week following each treatment.
    - Clothing soiled with fecal matter or urine must be washed immediately and separately from other clothing.
    - Caregivers should wear gloves and barrier gowns when handling bodily fluids to avoid contamination. Caregivers must wash hands after handing body fluids.
    - Use the same toilet each time you use the bathroom in your home. Sit down to urinate. Flush the toilet with the lid down three times after each use. Wash your hands thoroughly using the bathroom.
- If you are sexually active with a female partner of childbearing potential, use a latex condom and a second method of birth control during treatment AND for 6 months after stopping this medication.

The Nuclear Medicine Department is located on the 3rd floor of the Huntsman Cancer Hospital

Revision Date: 11/4/2015
Owner: Delynn Strate, Manger Nuclear Medicine

Patient Instruction for Xofigo Therapy
University of Utah Healthcare
Huntsman Cancer Institute

Please follow the precautions listed below after the Xofigo dose is given.

- **Be sure you keep your blood cell count monitoring appointments** and report to a healthcare provider any signs of low blood cell counts (such as shortness of breath and tiredness in the case of anemia), and report any signs of bleeding (such as bruising) or infection (such as fever).
- **Stay well hydrated** and report any signs of dehydration, or urinary or kidney problems.
- **There are no restrictions regarding contact** with any other people after receiving a Xofigo dose.
- **Bathroom hygiene is important.** Radioactivity is present in urine and feces for some time after treatment. Be sure to practice good personal hygiene while on treatment with Xofigo and for at least 1 week after the last injection. After going to the bathroom, be sure to wash your hands thoroughly and flush the toilet several times. Promptly clean up spilled bodily waste, wearing gloves when you clean. Dispose of gloves as trash and place in plastic bags to prevent accidental access. Wash your hands when you are finished. If bodily waste gets into clothing, promptly wash it separately from other laundry.
- **Use condoms** and make sure female partners who can have children use highly effective birth control methods during and for a minimum of 6 months after treatment with Xofigo.
- **The most common side effects of Xofigo include** nausea, diarrhea, vomiting, swelling of the arms or legs (peripheral edema), and low blood cell counts. Tell your healthcare provider if you have any side effects that bother you or do not go away.
- If you have any questions please call the Nuclear Medicine Clinic at (801) 581-2370. You can also call the Radiation Oncology Front Desk at (801) 581-2396 and ask to speak to a nurse or contact your study coordinator. If there is an emergency please dial 911.

Appendix 17.5 ECOG/KPS Conversion

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on 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—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare 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 of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.
**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960:11:7-33.