

Full Study Protocol and Statistical Analysis Plan

Study Title: A Phase 2 Randomized Study comparing Radium Ra 223 dichloride + Enzalutamide with Enzalutamide alone in Men with Metastatic Castration Refractory Prostate Cancer

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Protocol name: Radium Ra 223 Dichloride + Enzalutamide in mCRPC

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Principal Investigator: Neeraj Agarwal, MD

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Enzalutamide with Enzalutamide alone in Men with
Metastatic Castration Refractory Prostate Cancer**

Lead Trial ID: HCI68770/ IRB# 68770

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LIST OF ABBREVIATIONS

Abbreviation or Term ¹	Definition/Explanation
AE	Adverse event
AR	Androgen receptor
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
β-HCG	Beta-human chorionic gonadotropin
BP	Blood pressure
BUN	Blood urea nitrogen
Ca ⁺⁺	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
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
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ECG	Electrocardiogram
Eg	Exempli gratia (for example)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HR	Heart rate
hr	Hour or hours

Abbreviation or Term¹	Definition/Explanation
i.e.	Id est (that is)
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
MedRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
NIST	US National Institute of Standards of Technology
PFS	Progression Free Survival
PO	Per os (administered by mouth)
PR	Partial response
RBC	Red blood cell
QD	Once daily
SAE	Serious adverse event
SD	Stable disease
T _{max}	Time of maximum observed concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

¹ 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 Randomized Study comparing Radium Ra 223 dichloride + Enzalutamide with Enzalutamide alone in Men with Metastatic Castration Refractory Prostate Cancer
Short Title	Radium Ra 223 dichloride + Enzalutamide with Enzalutamide alone in mCRPC
Protocol Number	IRB # 68770
IND	IND Exempt (121340)
Phase	Phase 2
Design	Open label, randomized two arm study in men with progressive metastatic CRPC who are candidates for treatment with enzalutamide alone or enzalutamide + Radium Ra 223 dichloride
Study Duration	3.5 years
Study Center(s)	Single-center - Huntsman Cancer Institute
Objectives	<p>Primary:</p> <ol style="list-style-type: none"> 1. To measure the difference between the levels of markers of bone formation (Procollagen Type 1 intact N-terminal Propeptide [NTP] and bone alkaline phosphatase [BAP]) and resorption (N-telopeptide [NT], C-Telopeptide beta-cross linked [CTB], pyridinoline) in serum collected at baseline (C1D1), C3D1, C5D1, EOT and at disease progression (whichever comes earlier) in two arms. 2. To establish safety and feasibility of combining enzalutamide and radium-223. <p>Secondary: The secondary objectives will compare the two arms for the following:</p> <ol style="list-style-type: none"> 1. Time to progression in serum PSA, total ALP concentrations, and radiological progression. 2. Response rates by serum PSA, total ALP concentrations. 3. Time to first skeletal related event. 4. Percent change in opioid use (morphine equivalent) during protocol treatment. 5. Overall Survival at 2 years post enrollment.
Number of Subjects	<p>47 patients (50 total to account for any inevaluable patients).</p> <p>Combination Arm – 35 evaluable patients (27 randomized patients + 8 patients enrolled prior to randomization who will be used for secondary and exploratory analyses only).</p> <p>Control Arm (enzalutamide alone) – 12 evaluable patients.</p>

Diagnosis and Main Eligibility Criteria	<ul style="list-style-type: none"> • Histologically documented adenocarcinoma of the prostate. • Metastatic disease as evidenced by bony metastases on baseline bone scan and / or computed tomography (CT) scan or MRI of the abdomen and pelvis. • Castration resistant prostatic adenocarcinoma. Subjects must have castrate levels of testosterone (< 50 ng/dL) achieved by orchiectomy or LHRH agonist or antagonist therapy. • Evidence of disease progression on or after the most recent systemic treatment. • Prior chemotherapy with docetaxel and cabazitaxel allowed. • No known brain metastases, malignant pleural effusions, or malignant ascites. • No visceral metastases • No prior treatment with radium-223 or enzalutamide. • No pathologic long-bone fractures, imminent pathologic long-bone fracture (cortical erosion on radiography > 50%) or spinal cord compression.
Study Product, Dose, Route, Regimen and Duration	<p>Combination Arm: Radium Ra 223 dichloride 55 kBq/kg body weight every 4 weeks with daily enzalutamide 160 mg PO for 6 cycles (each cycle comprises 4 weeks).</p> <p>Control Arm: Single agent enzalutamide 160mg PO daily for 6 cycles.</p>
Statistical Methodology	<p><u>Primary Bone Marker Analysis</u></p> <p>Concomitant treatment with radium-223 (a bone targeting agent) and enzalutamide (a tumoricidal agent) is expected to decrease the level of N-telopeptides. As mentioned in the Background Section, serum N-telopeptides levels are inversely associated with overall survival, based on data from the SWOG 0421 trial. The primary endpoint for statistical analysis for this study will be the change in log 2 N-telopeptides from baseline to EOT or at disease progression (whichever comes earlier) between the randomization groups. If a bone marker test is missed at a given time point, every effort will be made to obtain the bone marker levels as early as possible. If two subsequent bone marker tests are missed, patient will be excluded from the analysis for the primary endpoint. Equality of the change in log2 N-telopeptides between the treatment arms will be tested using an ANCOVA model with treatment group as the primary predictor and initial log 2 N-telopeptides as adjustment variable. As a sensitivity analysis an F-test for equality of variance of final log2 N telopeptides will be performed. If the null</p>

	<p>hypothesis is rejected at the 0.1 significance level an additional ANCOVA model allowing for unequal variances will be fit.</p> <p><u>Additional Analyses of the Primary Endpoint</u></p> <p>Separate analysis in the combined population will be performed in subjects treated with enzalutamide + radium-223 and subjects treated with enzalutamide alone. If a bone marker test is missed at a given time point, every effort will be made to obtain the bone marker levels as early as possible. If two subsequent bone marker tests are missed, patient will be excluded from the analysis. Based on the data from the SWOG 0421 study, the estimated baseline mean and standard deviation of log2 N-telopeptides are 3.95 nM and 1.14 nM respectively. We further assume the Pearson correlation of baseline and follow up N-telopeptides is 0.50. With 35 evaluable subjects there will be 80% power to detect a change of 0.556 in log2 N-telopeptides using a paired t-test. Extrapolating from SWOG0421, a decrease of 0.556 in log2 N-telopeptide concentration would translate into an approximate 20% increase in median overall survival.</p> <p><u>Primary Safety Analyses</u></p> <p>An overall proportion of subjects with grade 3 or higher hematologic adverse events significantly higher than those reported for the radium-223 arm of Parker et al. (2013) would be evidence of unacceptable toxicity.^{8,19}. In that study the sum of the proportion of subjects with grade 3+ anemia, thrombocytopenia, or neutropenia is 21%. An exact binomial test will be performed at the one sided 0.05 significance level comparing the proportion of subjects with one or more of grade 3+ anemia, thrombocytopenia, or neutropenia to 21%. With a safety population of 35 evaluable patients, 13 or more patients with one or more of grade 3+ anemia, thrombocytopenia, or neutropenia would indicate an unacceptable hematologic adverse event rate.</p> <p>Exact 90% confidence intervals will be calculated for adverse events (AEs) and serious AEs (SAEs). With 35 evaluable patients an exact 90% confidence interval for an AE will extend no more than 17.5% from the observed proportion, and there is a 90% probability that an adverse event with a probability of 6.4% will be observed at least once.</p> <p><u>Secondary Endpoint Analyses</u></p> <p>All other statistical analyses will be descriptive in nature. Please refer to section 10.2 for additional detail.</p>
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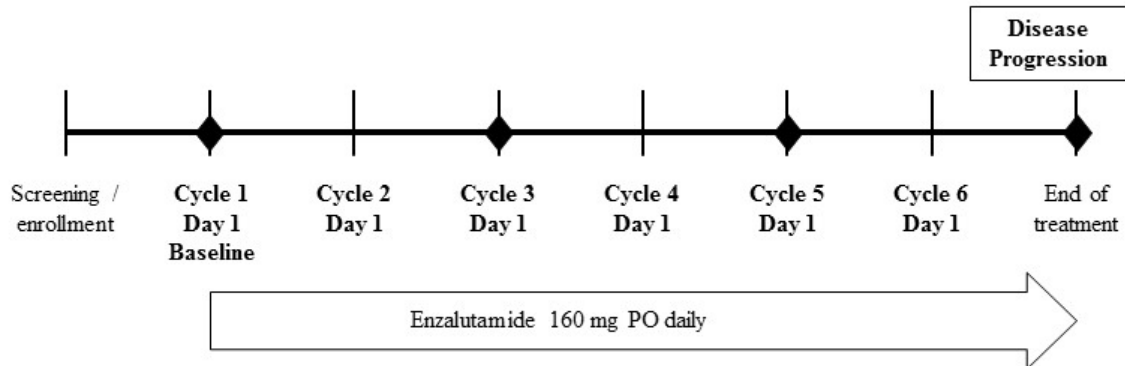
SCHEMA

Metastatic CRPC Patients.

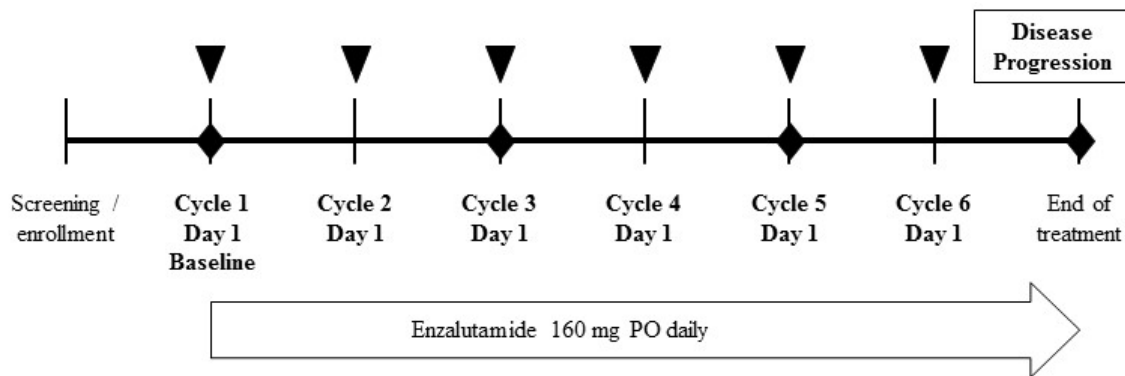
Previously received docetaxel or are not healthy enough per clinical judgment or declined to receive it.

Eligible patients randomized 1:2 (12 patients in the control arm and 27 patients in the combination arm).

Control Arm: Single agent enzalutamide



Combination Arm: Enzalutamide + Radium-223



- ◆ = Serum collection for bone markers at baseline (C1D1 before treatment), C3D1, C5D1, EOT and Disease Progression (whichever comes first).
- ▼ = Radium-223 administration (50 kBq/kg bolus IV and 55 kBq/kg body weight after the implementation of the NIST update).

1 OBJECTIVES

We hypothesize that simultaneous treatment with radium-223 and enzalutamide will decrease bone metabolism markers compared to enzalutamide alone and the combination will be safe and feasible. This hypothesis will be tested through the following aims:

1.1 Primary Objectives and Endpoint

- 1.1.1** To measure the difference between levels of markers of bone formation (Procollagen Type 1 intact N-terminal Propeptide [NTP] and bone alkaline phosphatase [BAP]) and resorption (N-telopeptide [NT], C-Telopeptide beta-cross linked [CTB], pyridinoline) in serum collected at baseline (C1D1), C3D1, C5D1, EOT and at disease progression (whichever comes earlier) in men enrolled in this trial, and compare these levels in both arms.
- 1.1.2** To establish safety and feasibility of combining enzalutamide and radium-223.

1.2 Secondary Objectives and Endpoint

To compare the following objectives between the two arms:

- 1.2.1** Time to progression in serum prostate-specific antigen (PSA), total alkaline phosphatase (ALP) concentrations, and radiological progression.
- 1.2.2** Response rates by serum PSA and total ALP concentrations.
- 1.2.3** Time to first skeletal related event.
- 1.2.4** Percent change in opioid use (morphine equivalent) during protocol treatment.
- 1.2.5** Overall Survival at 2 years post enrollment.

2 BACKGROUND

The therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) has been revolutionized by the arrival of multiple novel agents in the past 2 years. Androgen axis inhibitors including abiraterone acetate and enzalutamide, immunotherapy in the form of sipuleucel-T, and a radiopharmaceutical, radium-223, have all yielded incremental extensions of survival. Improved survival with radium-223 and enzalutamide underscores the importance of bone targeting and androgen pathway inhibition in mCRPC.

2.1 Rationale for using enzalutamide and radium-223

Enzalutamide (MDV 3100) is a novel AR antagonist that binds to androgen receptors with an eight-times higher affinity than bicalutamide and reduces the efficiency of nuclear translocation of the androgen receptor, DNA binding to

androgen response elements, and recruitment of coactivators by the androgen receptor.¹ In contrast to bicalutamide, enzalutamide has no known agonist activity when AR is over-expressed. In a phase III trial of men with CRPC with prior docetaxel therapy, enzalutamide, when compared to placebo, significantly improved overall survival (18.4 vs 13.6 months; $p < 0.001$), leading to its regulatory approval in this setting.² Another phase III trial of enzalutamide in chemotherapy-naïve men with CRPC has completed accrual and results are awaiting publication.

Radium-223 is a calcium-mimetic radiopharmaceutical that accumulates in bones and emits alpha radiation from radium-223 decay, releasing relatively high energy with a narrow range (2 to 10 cells).³ Following promising results in a phase II trial, the phase III ALSYMPCA trial was conducted in mCRPC patients with symptomatic bone metastases who either had received or were ineligible for docetaxel.⁴ 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).⁵ 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).⁶ 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.⁷ Another dose-finding phase II trial demonstrated more frequent PSA and serum alkaline phosphatase declines with higher doses up to 80 kBq/kg.⁸

Although, improved survival with these novel agents is very encouraging, no data exist from randomized trials on how to optimally combine these agents, and the effect of rationale combination of these agents on therapeutic outcomes. We hypothesize that combinatorial regimen of radium-223 and enzalutamide will improve bone health, delay bone events, and improve pain and survival outcomes by simultaneously targeting bone metastases and androgen signaling.

2.2 Specific rationale for using markers of bone turnover/metabolism as a primary endpoint

Bone metabolism is distinguished by two opposing activities: the formation of new bone by osteoblasts, and the resorption of old bone by osteoclasts. These processes are tightly coupled in space and time. Ultimately, bone mass is dependent upon the balance between formation and resorption. In prostate cancer, this homeostatic balance tips such that osteoblastic activity predominates, resulting in sclerotic bone metastases. Bone metastasis is a very common event in patients with prostate cancer and is a frequent source of morbidity, including bone pain or fracture. Many prostate cancer patients with bone metastases have elevated circulating biochemical markers of bone metabolism, including markers for osteoblast and osteoclast activity. These serum-based biomarkers have been explored as indicators of bone turnover for their potential as prognostic and / or predictive variables.^{9,10} Prior studies have suggested that elevated markers of bone turnover are strongly prognostic for poor survival in castration resistant prostate cancer patients,¹¹ and may predict outcome with systemic therapy.¹²⁻¹⁴

SWOG 0421 was a large placebo-controlled phase III study of docetaxel with or without the endothelin antagonist atrasentan in castration resistant prostate cancer patients with skeletal metastases. Disappointingly, we did not observe any survival advantage for the docetaxel + atrasentan arm.¹⁵ However, as a translational science component of that randomized trial, pre-treatment and serial serum markers of bone turnover were prospectively assessed to validate their prognostic and predictive value in these castration-resistant patients. Markers of bone resorption (N-telopeptide, NTX & Pyridinoline, PYD) and bone formation (C-terminal collagen propeptide, CACP & bone alkaline phosphatase, BAP) were measured. Cox regression models were developed for overall survival based on baseline bone markers (log2 scale), adjusted for potentially confounding clinical variables (including PSA, bisphosphonate use, age, race, performance status, Gleason score, and pain score, among others). The effect of treatment on bone marker levels in week 9 (as compared to baseline) was explored to find an association between a change in marker levels and overall survival outcomes. A Cox model was fit with main effects and Bone Marker x Treatment interaction, adjusted for clinical variables, to assess the predictive value of atrasentan on overall survival. Of 1038 patients enrolled in SWOG 0421, 855 (91%) had baseline serum submitted, of which 778 samples (75%) were usable and subsequently analyzed. The bone turnover values (median; range) were as follows: NTX (14 nM; 9.3-23.9), BAP (64.7 u/L; 35-164), CACP (9.5 ng/mL; 6.5-17.4), & PYD (2.8 nmol/L; 2.2-3.9).

The significant prognostic role of elevated markers of bone turnover (> median value) on overall survival is shown in Table 1 below. Hazard ratios are reported for a 2-fold increase in bone metabolism markers. Follow-up analysis revealed that patients with high marker levels (ie, upper 25%-ile across all markers) not only have a very poor prognosis (HR = 4.3, $p < 0.001$) but also appear to have a significant survival benefit from atrasentan (interaction-HR = 0.33; $p = 0.002$), even with highly conservative statistical analysis including Bonferroni adjustment. Of the 778 patients 6% (47) had a complete set of baseline markers measurements. The HR in the high marker group was estimated at 0.34 (95% CI: 0.13, 0.89); this compares with a HR of 1.04 (95% CI: 0.86, 1.25) in the low marker group.¹⁶

Table 1: Prognostic Value of Markers of Bone Turnover

Biomarker	Hazard Ratio (95% CI)	Median Survival, months (≤ median BMB value vs. > median)	p- value*
BAP (u/l)	1.26 (1.19, 1.35)	22.8 vs. 15.4	< 0.001
CACP (ng/ml)	1.38 (1.27, 1.5)	24.5 vs. 14.6	< 0.001
NTx (nM)	1.43 (1.31, 1.57)	22.4 vs. 15.5	< 0.001
PYD (nmol/l)	1.49 (1.32, 1.7)	20.3 vs. 15.3	< 0.001
Significance was set at ≤ 0.006 (Bonferroni adjustment to control overall 2-sided error rate across 4 tests at 0.05)			

There was also strong evidence for a significant association between the change in bone marker concentrations from baseline to week 9 and overall survival for all bone markers (Table 2).

Table 2: Association between overall survival and the change from baseline to week 9 in the (log2) bone marker concentration, adjusted for baseline bone marker concentration and bisphosphonate use

Marker	Hazard Ratio	95% CI	P-value
BAP (u/l)	1.33	(1.16, 1.51)	< 0.001
CICP (ng/ml)	1.46	(1.23, 1.72)	< 0.001
NTx (nM)	1.45	(1.20, 1.75)	< 0.001
PYD (nmol/l)	1.59	(1.25, 2.02)	< 0.001

These results demonstrate that baseline serum levels of bone metabolism markers have significant independent overall survival prognostic value in patients with castration resistant disease. In addition, patients with elevated serum bone metabolism markers levels appeared to preferentially benefit from a novel systemic agent such as atrasentan.

Presently, it is unclear whether these same observations will be observed in a somewhat different therapeutic context, i.e. in men with mCRPC being treated with radium-223 plus enzalutamide. This proposed phase II trial of a combinatorial regimen of radium-223 with enzalutamide provides a unique opportunity to directly address this important clinical question.

As noted above, 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), thereby targeting bone metastasis,¹⁷ and has been shown to improve survival and increases the time to first skeletal related event (SRE) when compared to placebo (median time to SRE 13.6 vs 8.4 months, respectively; P = 0.00046; HR = 0.610; 95% CI: 0.461, 0.807).¹⁸ These data support the notion that treatment with radium-223 will result in modulation of bone metabolism, and thus improve bone and survival outcomes.

We hypothesize that simultaneous treatment with radium-223 and enzalutamide will significantly decrease bone metabolism markers (thus improving bone and clinical outcomes) compared to enzalutamide alone, and will be safe and feasible.

3 DRUG INFORMATION

3.1 Radium Ra 223

3.1.1 Description

Radium Ra 223 dichloride, an alpha particle-emitting pharmaceutical, is a radiotherapeutic drug. It 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, $^{223}\text{RaCl}_2$, 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 in Xofigo (radium-223 dichloride; BAY 88-8223) is based on the primary standardization performed by the US NIST. The National Institute of Standards and Technology prepares the standard reference material (SRM) using an official dial setting (primary standardization) as published.²⁰ 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 standardization²⁰ and results obtained by other national metrology institutes (United Kingdom, Germany, Japan). After completion of the re-assessment, NIST reported their findings²¹ 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 4/25/2016. As of that date the FDA approved the regulatory variation submitted for Xofigo. The change in the numerical description of the patient's dose, product strength and labeled vial activity does not impact the safety or efficacy of Xofigo. The change in the NIST radium-223 standard has no impact on subjects; dose subjects are receiving, and will continue to receive.

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

3.1.2 Mechanism of Action

The active moiety of Radium Ra 223 dichloride is the alpha particle-emitting isotope radium-223, 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 the start of treatment. Osteosarcomas were not observed in dog studies. The presence of neoplastic changes, other than osteosarcomas, was also reported in 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 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 Radium Ra 223 dichloride in CRPC / HRPC patients with bone metastases was safe and 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 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 vs. 11.3 months, respectively).

In the ALSYMPCA study, the results of the interim analysis and the updated analysis also showed 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 $\geq 25\%$ increase compared to baseline / nadir) was statistically significantly longer in the radium-223 chloride group, 7.4 months compared to 3.8 months in the placebo group (HR = 0.167, 95% CI: 0.129, 0.217; $p < 0.00001$).
- Time to PSA progression (defined as a $\geq 25\%$ 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 $\geq 30\%$ or $\geq 50\%$ 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 group (3% and $< 1\%$ respectively).
- Subgroup survival analysis showed a consistent survival benefit for treatment with Radium Ra 223 dichloride, independent of total alkaline phosphatase, 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 ($\geq 10\%$) in patients receiving Radium Ra 223 dichloride were nausea, diarrhea, vomiting, and peripheral edema (Table 3). 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 ($\geq 10\%$) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia (Table 4). 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 3 shows adverse reactions occurring in $\geq 2\%$ of patients and for which the incidence for Radium Ra 223 dichloride exceeds the incidence for placebo.

Table 3: 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 4 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 4: Hematologic Laboratory Abnormalities

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

Hematologic Laboratory Abnormalities	Xofigo (n = 600)		Placebo (n = 301)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
	%	%	%	%
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, 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. Monitor patients oral intake and fluid status carefully and promptly treat patients who display signs or symptoms of dehydration or hypovolemia.

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 cancers have been 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 cancers (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-223 arm of the Phase 3 clinical trial reported in Parker et al. (2013),^{8,19} 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.

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 $\geq 1.5 \times 10^9/\text{L}$, the platelet count $\geq 100 \times 10^9/\text{L}$, and hemoglobin $\geq 10 \text{ g/dL}$. Before subsequent administrations of Radium Ra 223 dichloride, the ANC should be $\geq 1 \times 10^9/\text{L}$ and the platelet count $\geq 50 \times 10^9/\text{L}$. 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.

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 Enzalutamide

3.2.1 Clinical Experience with Enzalutamide

In the randomized clinical trial in patients with metastatic castration-resistant prostate cancer who had previously received docetaxel, patients received XTANDI 160 mg orally once daily (N = 800) or placebo (N = 399). The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. All patients continued androgen deprivation therapy. Patients were allowed, but not required, to take glucocorticoids. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids. All adverse events and laboratory abnormalities were graded using NCI CTCAE version 4.

The most common adverse drug reactions ($\geq 5\%$) reported in patients receiving XTANDI in the randomized clinical trial were asthenia / fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Grade 3

and higher adverse reactions were reported among 47% of XTANDI-treated patients and 53% of placebo-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 5 shows adverse reactions reported in the randomized clinical trial that occurred at a $\geq 2\%$ absolute increase in frequency in the XTANDI arm compared to the placebo arm.

Table 5: Adverse Reactions in the Randomized Trial

	XTANDI N = 800		Placebo N = 399	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions	50.6	9.0	44.4	9.3
Peripheral Edema	15.4	1.0	13.3	0.8
Musculoskeletal And Connective Tissue Disorders				
Back Pain	26.4	5.3	24.3	4.0
Arthralgia	20.5	2.5	17.3	1.8
Musculoskeletal Pain	15.0	1.3	11.5	0.3
Muscular Weakness	9.8	1.5	6.8	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0.0
Gastrointestinal Disorders				
Diarrhea	21.8	1.1	17.5	0.3
Vascular Disorders				
Hot Flush	20.3	0.0	10.3	0.0
Hypertension	6.4	2.1	2.8	1.3
Nervous System Disorders				
Headache	12.1	0.9	5.5	0.0
Dizziness	9.5	0.5	7.5	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7.4	6.6	4.5	3.8
Paresthesia	6.6	0.0	4.5	0.0
Mental Impairment Disorders	4.3	0.3	1.8	0.0

3.2.2 Efficacy

The efficacy and safety of XTANDI in patients with metastatic castration-resistant prostate cancer who had received prior docetaxel-based therapy were

assessed in a randomized, placebo-controlled, multicenter phase 3 clinical trial. The primary endpoint was overall survival. A total of 1199 patients were randomized 2:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 800) or placebo orally once daily (N = 399). All patients continued androgen deprivation therapy. Patients were allowed, but not required to continue or initiate glucocorticoids. Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event, or clinical progression), initiation of new systemic antineoplastic treatment, unacceptable toxicity, or withdrawal. Patients with a history of seizure, taking medicines known to decrease the seizure threshold, or with other risk factors for seizure were not eligible.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 41 to 92) and the racial distribution was 92.7% Caucasian, 3.9% Black, 1.1% Asian, and 2.1% Other. Ninety-two percent (92%) of patients had an ECOG performance status score of 0-1 and 28% had a mean Brief Pain Inventory score ≥ 4 . Ninety-one percent (91%) of patients had bone metastases and 23% had visceral involvement in the lung and / or liver. Fifty-nine percent (59%) of patients had radiographic evidence of disease progression and 41% had PSA-only progression on study entry. All patients had received prior docetaxel-based therapy and 24% had received two cytotoxic chemotherapy regimens. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

The pre-specified interim analysis at the time of 520 events showed a statistically significant improvement in overall survival in patients on the XTANDI arm compared to patients on the placebo arm (Table 6).

Table 6. Overall Survival of Patients Treated with Either XTANDI or Placebo (intent-to-Treat Analysis)

	XTANDI N=800	Placebo N=399
Number of Deaths (%)	308 (38.5%)	212 (53.1%)
Median Survival (months) (95% CI)	18.4 (17.3, NR)	13.6 (11.3, 15.8)
P-value	< 0.0001	
Hazard Ratio (95% CI)	0.63 (0.53, 0.75)	

3.2.3 Pharmacokinetics and Drug Metabolism

The pharmacokinetics of enzalutamide and its major active metabolite (N-desmethyl enzalutamide) were evaluated in patients with metastatic castration-resistant prostate cancer and healthy male volunteers. The plasma enzalutamide pharmacokinetics are adequately described by a linear two-compartment model with first-order absorption.

Absorption

Following oral administration (XTANDI 160 mg daily) in patients with metastatic castration-resistant prostate cancer, the median time to reach maximum plasma enzalutamide concentrations (C_{max}) is 1 hour (range 0.5 to 3 hours). At steady state, the plasma mean C_{max} values for enzalutamide and N-desmethyl enzalutamide are 16.6 µg/mL (23% CV) and 12.7 µg/mL (30% CV), respectively, and the plasma mean predose trough values are 11.4 µg/mL (26% CV) and 13.0 µg/mL (30% CV), respectively.

With the daily dosing regimen, enzalutamide steady state is achieved by Day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady state, enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg.

A single 160 mg oral dose of XTANDI was administered to healthy volunteers with a high-fat meal or in the fasted condition. A high-fat meal did not alter the AUC to enzalutamide or N-desmethyl enzalutamide.

Distribution and Protein Binding

The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose is 110 L (29% CV).

Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin.

N-desmethyl enzalutamide is 95% bound to plasma proteins.

Metabolism

Following single oral administration of 160 mg of ^{14}C -enzalutamide, plasma samples were analyzed for enzalutamide and its metabolites up to 77 days post dose. Enzalutamide, N-desmethyl enzalutamide, and a major inactive carboxylic acid metabolite accounted for 88% of the ^{14}C -radioactivity in plasma, representing 30%, 49%, and 10%, respectively, of the total ^{14}C -AUC_{0-inf}.

In vitro, human CYP2C8 and CYP3A4 are responsible for the metabolism of enzalutamide. Based on *in vivo* and *in vitro* data, CYP2C8 is primarily responsible for the formation of the active metabolite (N-desmethyl enzalutamide).

Elimination

Enzalutamide is primarily eliminated by hepatic metabolism. Following single oral administration of 160 mg of ^{14}C -enzalutamide, 85% of the radioactivity is recovered by 77 days post dose: 71% is recovered in urine (including only trace amounts of enzalutamide and N-desmethyl enzalutamide), and 14% is recovered in feces (0.4% of dose as unchanged enzalutamide and 1% as N-desmethyl enzalutamide).

The mean apparent clearance (CL/F) of enzalutamide in patients after a single oral dose is 0.56 L/h (range 0.33 to 1.02 L/h).

The mean terminal half-life ($t_{1/2}$) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days). Following a single 160 mg oral dose of enzalutamide in healthy volunteers, the mean terminal $t_{1/2}$ for N-desmethyl enzalutamide is approximately 7.8 to 8.6 days.

Pharmacokinetics in Special Populations

Renal Impairment

A population pharmacokinetic analysis (based on pre-existing renal function) was carried out with data from 59 healthy male volunteers and 926 patients with metastatic castration-resistant prostate cancer enrolled in clinical trials, including 512 with normal renal function ($\text{CrCL} \geq 90 \text{ mL/min}$), 332 with mild renal impairment ($\text{CrCL} 60 \text{ to} < 90 \text{ mL/min}$), 88 with moderate renal impairment ($\text{CrCL} 30 \text{ to} < 60 \text{ mL/min}$), and 1 with severe renal impairment ($\text{CrCL} < 30 \text{ mL/min}$). The apparent clearance of enzalutamide was similar in patients with pre-existing mild and moderate renal impairment ($\text{CrCL} 30 \text{ to} < 90 \text{ mL/min}$) compared to patients and volunteers with normal renal function. The potential effect of severe renal impairment or end stage renal disease on enzalutamide pharmacokinetics cannot be determined as clinical and pharmacokinetic data are available from only one patient.

Hepatic Impairment

The plasma pharmacokinetics of enzalutamide and N-desmethyl enzalutamide were examined in volunteers with normal hepatic function ($N = 16$) and with pre-existing mild ($N = 8$, Child-Pugh Class A) or moderate ($N = 8$, Child-Pugh B) hepatic impairment. XTANDI was administered as a single 160 mg oral dose. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild or moderate baseline hepatic impairment compared to volunteers with normal hepatic function. Clinical and pharmacokinetic data are not available for patients with severe hepatic impairment (Child-Pugh Class C).

Body Weight and Age

Population pharmacokinetic analyses showed that weight (range: 46 to 163 kg) and age (range: 41 to 92) do not have a clinically meaningful influence on the exposure to enzalutamide.

Gender

The effect of gender on the pharmacokinetics of enzalutamide has not been evaluated.

Race

The majority of patients in the randomized clinical trial were Caucasian (> 92%). There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.

3.2.4 Summary of Non Clinical Experience

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the *in vitro* mouse lymphoma thymidine kinase (Tk) gene mutation assay or the *in vivo* mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4- and 13-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

Refer to the Investigator's Brochure for additional information about enzalutamide.

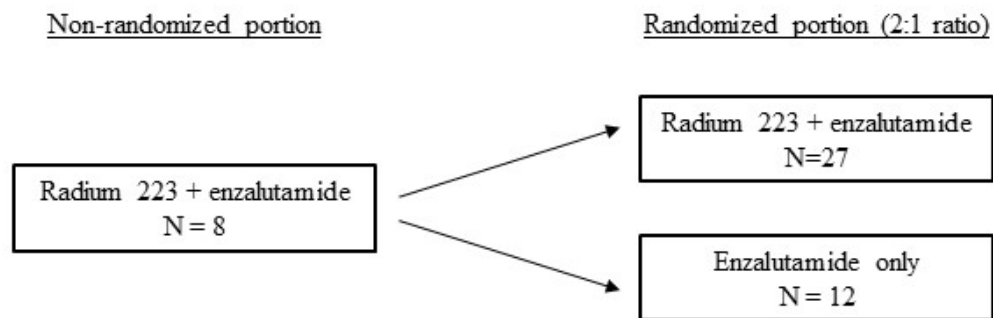
4 STUDY DESIGN

4.1 Description

This is a phase 2, open label, randomized, two arm study in men with progressive metastatic CRPC who have previously received docetaxel or are ineligible for docetaxel and who are candidates for treatment with enzalutamide alone or enzalutamide in combination with radium-223. The study will assess the difference between the combinatorial treatment and enzalutamide alone on the bone metabolism markers, including the decrease in N-telopeptide levels (i.e. decrease of 0.603 in log₂ N-telopeptides) from baseline to after 6 months of protocol treatment, as well as assess the safety and feasibility of the combinatorial regimen.

The study has an initial non-randomized single arm portion (enzalutamide + radium-223, n = 8 patients) followed by a randomized (2:1) portion comparing enzalutamide + radium-223 versus enzalutamide alone (n = 39 patients) as shown in Figure 1 below.

Figure 1: Initial Single Arm Non-Randomized Design Changed to Two Arm Randomized 2 to 1 Design



Only those patients enrolled on the randomized portion of the trial will be used for primary endpoint analysis. Patients enrolled on the non-randomized portion will be used for secondary and exploratory analyses only.

4.2 Number of Patients

Forty-seven patients (50 total to account for any inevaluable patients) will be enrolled in the study. Twelve patients will be enrolled on the control arm (enzalutamide alone) and thirty-five patients (27 randomized patients + 8 patients enrolled prior to randomization who will be used for secondary and exploratory analyses only) will be enrolled on the combination arm (enzalutamide + radium-223) .

4.3 Number of Study Centers

This is a single-center study to be conducted at Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah.

4.4 Duration

It is expected that all patients will be accrued within 18 months. Subjects will remain on study treatment for up to 6 months. Patients will be followed for a total of two years from the first day of protocol treatment or until death, whichever occurs earlier. The total study duration for a patient is expected to be 2 years from the time of 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 _____ Histologically documented adenocarcinoma of the prostate.
- 5.1.2 _____ Men at least 18 years of age and life expectancy of ≥ 6 months.
- 5.1.3 _____ ECOG performance status ≤ 2 .
- 5.1.4 _____ Metastatic disease as evidenced by both lymphadenopathy and bony metastases or just bony metastases on baseline bone scan and / or computed tomography (CT) scan or MRI of the abdomen and pelvis within 28 days of registration. Chest imaging is only required if clinically indicated or if there is known disease in the chest.
- 5.1.5 _____ Castration resistant prostatic adenocarcinoma. Subjects must have castrate levels of serum testosterone (< 50 ng/dL) achieved by orchiectomy or LHRH agonist or antagonist therapy.
- 5.1.6 _____ Previously received docetaxel or are not healthy enough per clinical judgment or declined to receive it.
- 5.1.7 _____ Evidence of disease progression on or after the most recent systemic treatment defined by one of the following criteria:

PSA: Increasing serum PSA levels as defined by the PCWG2, determined by 2 consecutive measurements (compared to a baseline or nadir value). If the third measurement is below the second, then a fourth measurement must be greater than the second. The confirming third or fourth measurement must be ≥ 2 ng/mL. PSA progression must have occurred within 15 months of registration (with at least 7 days between each PSA measurement). Additionally, the PSA progression as described above should have occurred during or after the most recent systemic treatment for prostate cancer.

Measurable disease: $\geq 20\%$ increase in the sum of the short axis diameter of all measurable lymph nodes or the development of

any new measurable lymphadenopathy by RECIST 1.1 and PCWG2 criteria.

Non-measurable disease:

Lymph node disease: Appearance of 1 or more new lymphadenopathy, and / or unequivocal worsening of non-measurable disease when compared to imaging studies acquired during castration therapy or against the pre-castration studies if there was no response.

Bone disease: Appearance of 2 or more new areas of abnormal uptake on bone scan when compared to imaging studies acquired during castration therapy or against the pre-castration studies if there was no response. Increased uptake of pre-existing lesions on bone scan does not constitute progression.

5.1.8 _____ Symptomatic Bone metastases.

5.1.9 _____ Adequate hematologic, renal, and liver function as evidenced by the following:

1. White blood cell (WBC) $\geq 3,000$ cells/ μ L
2. Absolute neutrophil count (ANC) $\geq 1,500$ cells/ μ L
3. Platelet Count $\geq 100,000$ cells/ μ L
4. Hemoglobin (Hgb) ≥ 10.0 g/dL
5. Total Bilirubin ≤ 1.5 x upper limit of normal (ULN)
6. Creatinine ≤ 1.5 X ULN
7. Aspartate aminotransaminase (AST, SGOT) ≤ 2.5 x ULN
8. Alanine aminotransaminase (ALT, SGPT) ≤ 2.5 x ULN
9. Albumin > 25 g/L
10. Creatinine clearance > 30 ml/min

Transfusion of blood products are not allowed to normalize blood parameters within 4 weeks of the first Radium treatment.

5.1.10 _____ Men must agree to use adequate contraception 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, men who are sexually active must agree to use condoms and their female partners of reproductive 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 have signed an approved consent form that conforms to federal and institutional guidelines to ensure compliance with HIPAA regulations.

5.2 Exclusion Criteria

Yes/No (Response of “yes” = patient ineligible)

- 5.2.1 _____ The presence of known brain metastases, malignant pleural effusions, or malignant ascites. Brain MRI is required at screening only if clinically indicated.
- 5.2.2 _____ Visceral metastases as assessed by chest, abdominal, or pelvic computed tomography (CT) (or other imaging modality).
- 5.2.3 _____ 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.
- 5.2.4 _____ Prior treatment with enzalutamide.
- 5.2.5 _____ Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than the protocol based treatment. LHRH agonist or antagonist therapy, and supportive non-cancer directed therapies like bisphosphonates or denosumab are allowed.
- 5.2.6 _____ Prior cytotoxic chemotherapy with the exception of docetaxel or cabazitaxel. Treatment with docetaxel or cabazitaxel must be discontinued ≥ 4 weeks from the time of enrollment, and recovery of AEs to grade 1 or baseline (however, ongoing neuropathy is permitted).
- 5.2.7 _____ Major surgery within 30 days prior to start of study drug.
- 5.2.8 _____ Current, untreated pathologic long-bone fractures or imminent long-bone fractures (cortical erosion on radiography $> 50\%$).
- 5.2.9 _____ Prior hemi-body external radiotherapy. Subjects who received other types of prior external radiotherapy are allowed provided that bone marrow function is assessed and meets the protocol requirements for hemoglobin, ANC, and platelets.
- 5.2.10 _____ Use of biologic response modifiers, such as granulocyte macrophage colony-stimulating factor (GM-CSF) or granulocyte colony-stimulating factor (G-CSF) within 4 weeks prior to screening.
- 5.2.11 _____ Lymphadenopathy exceeding 3 cm in short-axis diameter.
- 5.2.12 _____ Any size pelvic lymphadenopathy if it is thought to be a contributor to concurrent hydronephrosis.

- 5.2.13** _____ Current or imminent spinal cord compression based on clinical findings and / or magnetic resonance imaging (MRI). Treatment should be completed for spinal cord compression.
- 5.2.14** _____ Any other serious illness or medical condition in the opinion of the investigator, such as but not limited to:
- Any Grade ≥ 2 infection as defined by NCI-CTCAE version 4.03.
 - Cardiac failure New York Heart Association (NYHA) III or IV.
 - Crohn's disease or ulcerative colitis.
 - Bone marrow dysplasia.
 - Fecal incontinence.
- 5.2.15** _____ Concomitant use of narrow therapeutic index drugs that are metabolized by CYP3A4 (i.e. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (phenytoin, warfarin), and CYP2C19 (S-mephenytoin). [Note: Patients on stable doses of anti-coagulation with warfarin and fentanyl will be eligible, as long as they are monitored closely with additional INR monitoring]. A complete list can be found at: <http://medicine.iupui.edu/clinpharm/ddis/main-table/>.
- 5.2.16** _____ Any infection requiring parenteral antibiotic therapy or causing fever (temperature $> 100.5^{\circ}\text{F}$ or 38.1°C) within 1 week prior to registration.
- 5.2.17** _____ Concurrent other malignancy with the exception of: a) cutaneous squamous cell and basal carcinomas, b) adequately treated stage 1-2 malignancy, c) adequately treated stage 3-4 malignancy that had been in remission for ≥ 2 years at the time of registration.
- 5.2.18** _____ Inability to comply with the protocol and/or not willing or not available for follow-up assessments.
- 5.2.19** _____ Any medical intervention or other condition which, in the opinion of the Principal Investigator could compromise adherence with study requirements or otherwise compromise the study's objectives.

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

Investigator Signature

Date

Time

6 TREATMENT PLAN

6.1 Administration Schedule

1 cycle = 28 days

Repeat for a total of 6 cycles

Control Arm:

Enzalutamide 160 mg will be orally administered once a day (continuously) for 6 cycles.

Combination Arm:

Radium Ra 223 dichloride, 55 kBq/kg** body weight, will be administered as a bolus intravenous (IV) injection (up to 1 minute) on Day 1 of each cycle.

Enzalutamide 160 mg will be orally administered once a day (continuously).

**** The dose of radium was 50 kBq/kg body weight prior to implementation of the NIST update.**

6.2 Radium Ra 223 Dichloride Treatment

6.2.1 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 ($^{223}\text{RaCl}_2$) for IV administration. It should not be diluted or mixed with any solutions. Each vial is supplied for single use only.

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 6.0-8.0. The radioactive concentration at the reference date is 1100 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 (table 7).

**** The radioactive concentration at the reference date was 1000 kBq/mL prior to implementation of the NIST update.**

Radium Ra 223 dichloride will be obtained through commercial supply. It is manufactured by Algeta's contract manufacturer: Institute for Energy Technology, Isotope laboratories, Kjeller, Norway. The product is produced according to Good Manufacturing Practice (GMP). The product will be delivered in a glass vial, ready-to-use with a certified activity. 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 calibration 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 to 8 °C) up to 40 °C. In addition, it has been shown that the product quality is not jeopardized upon freezing.

**** The volume per vial (6 mL) corresponded to 6.0 MBq prior to implementation of the NIST update.**

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.

6.2.2 Preparation and Administration

Radium Ra 223 dichloride, 55 kBq/kg body weight (50 kBq/kg body weight prior to implementation of the NIST update), will be administered as a bolus intravenous (IV) injection (up to 1 minute) at intervals of every 4 weeks for up to 6 cycles.

6.2.2.1 Dose Calibration

Radium Ra 223 dichloride can be measured in a normal dose calibrator instrument, available at cancer centers and clinics certified to administer radium-223.

When written approvals for the use of Radium Ra 223 dichloride from the Radiation Protection Agency for the specific center have been received by the sponsor, a vial of Radium Ra 223 dichloride for technical use will be sent to the study center (a new reference vial will be sent to each center corresponding to the updated NIST reference material).

Each center must perform the Radium Ra 223 dichloride dial setting on their relevant dose calibrator(s) (upon notification by Bayer each center is required to update the dial settings to correspond to the new NIST standard). The current dial settings are to remain in effect until Bayer obtains FULL approval from the FDA for implementation. In preparation for implementation of the NEW dial setting, the clinical study center will receive a sealed vial labeled NIST standard containing a Radium Ra 223 dichloride solution for calibration only. The vial is identical to the vials used for study treatment. 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.

The updated NIST standardization became effective on 4/25/2016.

6.2.2.2 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 3.65 MBq or 0.0987 mCi (which corresponds to 50 kBq or 0.00135 mCi per kg body weight to a 73-kg adult), the calculated absorbed doses to the bone (osteogenic cells) is 4.2050 Gy (420.5 rad) and to the red marrow is 0.5066 Gy (50.66 rad). The calculated absorbed doses to the main excretory organs are 0.0265 Gy (2.65 rad) for the small intestine wall, 0.1180 Gy (11.8 rad) for the upper large intestine wall and 0.1696 Gy (16.96 rad) for the lower large intestine wall.

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

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

6.2.2.3 Dose Calculation

The dosage of Radium Ra 223 dichloride is 55 kBq (1.49 microcuries) per kg body weight (it was 50 kBq/kg or 1.35 μ Ci/kg prior to implementation of the NIST update).

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 (also see table 7).

Radium-223 is an alpha particle emitter with a physical $t_{1/2}$ of 11.4 days. The radioactive concentration at the reference date is 1100 kBq/mL (it was 1000 kBq/mL prior to implementation of the NIST update).

The volume to be administered for the current dose is calculated as follows:

$$\frac{\text{Body weight (kg)} \times \text{dose (55 kBq/kg body weight)}}{\text{DK factor} \times 1100 \text{ kBq/kg body weight}}$$

Table 7: Decay Correction Factor Table (DK factor)

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

6.2.2.4 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 in 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.

6.2.2.5 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 as a bolus intravenous (IV) injection (up to 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.

If a patient has travel or insurance difficulties with standard of care administration of Radium Ra 223 dichloride, the investigator may prescribe drug administration through the patient's local oncologist's office as long as source documentation of dosing calculations and administration can be provided to the study site. All study visits including day one procedures for each cycle, however, must be conducted at the study site. This option should only be used in rare situations for the benefit of the patient.

6.2.3 General Warning

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

6.2.4 Radiation Protection

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 8000 kBq or 216 μ Ci. In keeping with the As Low As Reasonably Achievable (ALARA) principle, for minimization of radiation exposure, it is recommended to minimize the time spent in radiation areas, to maximize the distance to radiation sources, and to use adequate shielding. Any unused product or materials used in connection with the preparation or administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations. The gamma radiation associated with the decay of radium-223 and its daughters allows for the radioactivity measurement of Radium Ra 223 dichloride and the detection of contamination with standard instruments.

6.2.5 Destruction and Return

At the end of the study, unused supplies of Ra 223 dichloride should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form. The certificate of destruction should be sent to Bayer.

6.3 Enzalutamide Treatment

6.3.1 How Supplied, Stored, Packaged and Labeled

Enzalutamide has the chemical name 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-N-methylbenzamide. It is a white to off-white solid that is insoluble in water and no salt forms are available at approximately pH 2 to 10. The drug substance is formulated in the surfactant caprylocaproyl polyoxylglycerides, or Labrasol®. The product will be supplied as white to off-white gelatin capsules containing 40 mg of enzalutamide.

6.3.2 Preparation and Administration

Patients will take 160 mg (4 capsules) of enzalutamide orally once daily. Study drug should be taken as close to the same time each day as possible. Study drug can be taken with or without food.

6.4 Accountability and Compliance

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

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

6.5 Concomitant Medications

All medication that is considered necessary for the subject’s welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator. Collection of opioid-use in morphine equivalent will be captured on the case report forms

Permitted

- Treatment with non-conventional therapies (e.g., herbs [with the exception of St. John’s Wart], acupuncture) and vitamin / mineral supplements is acceptable provided that, in the opinion of the investigator, such treatment will not interfere with the trial endpoints.
- Subjects may receive standard of care for any underlying illness.

- In the event of neutropenia, anemia, or thrombocytopenia, subjects may receive appropriate supportive care (e.g., transfusion, biologic response modifiers such as G-CSF or GM-CSF, prophylactic antibiotics, antifungals and/or antivirals, hematopoietic growth factors). This supportive care should not substitute a recommended dose modification. Once the recommended dose modification has occurred, prophylactic G-CSF or GM-CSF may be used per institutional standard of care to prevent future events.
- Blood transfusions and erythropoietin are allowed during the study period but not within 4 weeks prior to the first dose of Radium.
- Bisphosphonates and denosumab are allowed at screening and throughout the study. Concomitant use with these agents should be documented in the patient records.
- LHRH agonists and antagonists are allowed at screening and throughout the study. Concomitant use with these agents should be documented in the patient records.
- If surgery is required during study drug treatment, the surgeon needs to be notified that the patient has been treated with a radioactive product and adequate precautions for radioactive protection should be applied during the surgical procedure. The patient should continue with study treatment if considered safe in the treating Investigator's opinion.

Excluded concomitant therapies and medications

- Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than Radium Ra 223 dichloride.
- Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 4 weeks of trial entry (signing of the informed consent form).
- Clinical data indicate that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g., phenytoin, warfarin), and CYP2C19 (e.g., S-mephenytoin) should be avoided as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.
- Co-administration of a strong CYP2C8 inhibitor (e.g., gemfibrozil) increased the composite AUC_{0-∞} of enzalutamide plus its active metabolite in healthy volunteers; therefore, co-administration of enzalutamide with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of enzalutamide with strong CYP2C8 inhibitors cannot be avoided, reduce the enzalutamide dose to 80 mg once daily. If co-administration of the strong inhibitor is discontinued, the enzalutamide dose

should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

The effects of CYP2C8 inducers on the PK of enzalutamide have not been evaluated in vivo. Co-administration of enzalutamide with strong or moderate CYP2C8 inducers (e.g., rifampin) may alter the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended.

- The effects of CYP3A4 inducers on the PK of enzalutamide have not been evaluated in vivo. Co-administration of enzalutamide with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended. Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of enzalutamide and should be avoided if possible.

6.6 Protocol specified Duration of Therapy

Patients will receive up to 6 cycles of single agent enzalutamide or Radium Ra 223 dichloride and enzalutamide. If patients have a radium cycle delayed, the study visits will continue per the calendar and the dose will be missed. Treatment may be discontinued earlier if one of the following below criteria is met.

Subjects **must be withdrawn from the trial** (during protocol treatment and follow-up) for the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his / her own request or at the request of his / her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Subject is lost to follow-up.
- Anti-cancer therapy not prescribed by the study protocol is required.
- A treatment delay of more than 9 weeks between 2 injections of Radium Ra 223 dichloride.
- Disease Progression. During the protocol specified treatment, disease progression will be defined per PCWG2 progression criteria. After protocol defined therapy, the progression will be defined per clinical discretion of the treating clinician.
- Death.

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

- The subject is non-compliant with study drug, trial procedures, or both.

- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Development of a second cancer (other than superficial skin cancers, such as squamous cell carcinoma or basal cell carcinoma).
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 4.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

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

A subject who discontinues study participation prematurely for any reason is defined as a “dropout” if the subject has already been enrolled / registered.

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

Patients withdrawn prior to the C3D1 blood draw or determined to be not evaluable for the primary objectives may be replaced per investigators discretion.

7 TOXICITIES AND DOSEAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.03 for adverse event and serious adverse event reporting. A copy of the CTCAE Version 4.03 can be downloaded at <http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx>.

7.1 Dose Modifications Radium Ra 223 Dichloride

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 during the treatment period should occur at 4 weeks intervals (within a window of ± 7 days). If a patient requires a toxicity related dose delay of more than 9 weeks between 2 injections, then the patient must be discontinued from the study. If patients have a radium cycle delayed, the study visits will continue per the calendar and the dose will be missed. Dosing delays may be instituted under the following circumstances:

7.1.1 Myelosuppression

Treatment-related changes in hematology parameters may occur. Results from the CBC must be reviewed prior to drug administration on Day 1. The

following parameters must be met for the patient to proceed with treatment: platelets $\geq 50 \times 10^9/L$, ANC $\geq 1.0 \times 10^9/L$ and hemoglobin ≥ 8 g/dL.

- 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 within 4 weeks prior to the start of Radium treatment. Use of biologic response modifiers, such as G-CSF or GM-CSF, is allowed in the management of acute toxicity. After the appropriate dose modification for acute toxicity, G-CSF or GM-CSF may be used prophylactically for subsequent study treatments per institutional standard of care.

7.1.2 Gastrointestinal events

Diarrhea should be treated as per local practice. For Grade 3 or 4 diarrhea, 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. For Grade 3 nausea or grade 3 or 4 vomiting, 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.

7.1.3 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.

7.1.4 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.

7.1.5 Non-pathological fractures

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

7.1.6 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.

7.1.7 Any Other Toxicity

If a subject experiences any non-hematological CTCAE v4.03 Grade 4 toxicity, attributable to the study drugs, lasting more than 7 days despite adequate treatment, further study drug administration must be discontinued.

7.2 Dose Modifications Enzalutamide

Patients who experience a Grade 3 or greater toxicity attributed to enzalutamide, which cannot be ameliorated by the use of adequate medical intervention, may have their drug treatment interrupted for 1 week or until the toxicity grade improves to Grade 2 or lower severity. Enzalutamide may then be restarted at the same or a reduced dose (120 mg then 80 mg).

Protocol name: Radium Ra 223 Dichloride + Enzalutamide in mCRPC
Version Date: 02-06-17
Principal Investigator: Neeraj Agarwal, MD

8 STUDY CALENDAR

1 cycle = 28 days¹²

Examination	Screening ¹	C1	C2	C3	C4	C5	C6	End of Treatment ¹⁰	Survival Follow-up ¹¹
		Day 1	Day 1	Day 1 ^{6,7}	Day 1	Day 1 ⁷	Day 1 ^{6,7}		
Informed consent	X								
Medical history	X								
Eligibility criteria	X								
Vital signs (including weight)	X	X ¹⁴	X	X	X	X	X	X	
Physical examination	X	X ¹⁴	X	X	X	X	X	X	
ECOG performance status	X	X ¹⁴	X	X	X	X	X	X	
Hematology ^{2, 12}	X	X	X	X	X	X	X	X	
Chemistry ^{3, 12}	X	X	X	X	X	X	X	X	
Bone alkaline phosphatase (BAP) ⁴	X	X	X	X	X	X	X	X	
PSA ⁵	X	X	X	X	X	X	X	X	X
INR monitoring ¹³	X								
Imaging Studies (CT & bone scans) ⁶	X				X			X	X
Bone Markers ⁷		X		X		X		X ⁷	
Assessment of Adverse Events		X	X	X	X	X	X	X	
Enzalutamide ⁹		X	X	X	X	X	X		
Combination arm only: Radium Ra 223 dichloride ⁸		X	X	X	X	X	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.
- 2 Hematology includes CBC with differential and platelets. CBC must be completed within 2 weeks of study enrollment and prior to treatment (\pm 7 days) on day 1 of each cycle.
- 3 Chemistry includes Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total Bilirubin, Calcium, Carbon Dioxide, Creatinine, Chloride, Glucose, Potassium, Protein, Sodium, and Urea Nitrogen.
- 4 Bone alkaline phosphatase (BAP) should be done every four weeks until the end of treatment visit or disease progression (whichever comes earlier).
- 5 PSA is required within 28 days at screening, on day 1 of each cycle and at the end of treatment visit. PSA laboratory assessments should be performed every 4 – 6 weeks after the end of treatment visit until disease progression, or the start of another treatment.
- 6 CT and bone scans should be conducted at screening, end of cycle 3 (prior to C4D1 treatment), and at the end of treatment visit (4 weeks post last treatment). Follow-up scans will be performed as clinically indicated until documented PD per treating clinician or until the start of another treatment. Scans should include CT scan of abdomen and pelvis. Imaging of the chest is only required if clinically indicated.
- 7 Bone markers collected at baseline (C1D1), C3D1, C5D1, EOT and at disease progression (whichever comes earlier); to include procollagen Type 1 intact N-terminal Propeptide (NTP) and resorption (N-telopeptide [NT], C-Telopeptide beta-cross linked [CTB] and pyridinoline).
- 8 Radium Ra 223 dichloride 55 kBq/kg** on day 1 of every cycle for up to 6 cycles (** 50 kBq/kg prior to implementation of the NIST update).
- 9 Enzalutamide 160 mg daily.
- 10 End of Treatment visit should be conducted 4 weeks post C6D1.
- 11 For all patients who receive study treatment, follow-up for survival will occur approximately every 8 weeks following end of treatment or as clinically indicated for up to 2 years post enrollment or death.
- 12 All procedures for day 1 of each treatment cycle have a \pm 7 day window.
- 13 Subjects receiving concomitant medication with warfarin should have INR monitored more frequently as clinically indicated.
- 14 If the physical exam, ECOG score, and vital signs are done within 28 days of C1D1 they do not need to be repeated at this time-point.

9 CRITERIA FOR EVALUATION AND ENDPOINT

9.1 Assessment of bone metabolism:

Serum will be collected at various time points (at baseline and during protocol treatment). Markers of bone formation (C-terminal collagen propeptide, CACP and bone alkaline phosphatase, BAP) and resorption (N-telopeptide, pyridinoline) will be analyzed using standard technical methods at the ARUP lab at the University of Utah.

9.2 Assessment of clinical outcomes:

Clinical outcomes (time to PSA progression, time to first skeletal event, opioid usage, overall survival) will be assessed at various time points from the start of protocol treatment. Patients will be followed for a total of two years from the day of start of protocol treatment

9.3 Safety

All subjects who receive at least one dose of study treatment will be valid for the safety analysis.

All observations pertinent to the safety of the study treatment will be recorded and included in the final report.

All AEs whether considered drug-related or not, will be reported with a diagnosis, start / stop dates, action taken, whether treatment was discontinued, any corrective measures taken, outcome, and other possible causes. For all events, the relationship to treatment and the intensity of the event will be determined by the investigator.

This trial will use the NCI-CTCAE v4.03 criteria for assessment of toxicity and SAE reporting with regard to toxicity grade.

Safety variables may include but not limited to the following: laboratory changes (complete blood counts, electrolytes, chemistry, and coagulation), changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature), ECG, and, in some instances, changes in chest x-ray images, as produced at the investigator's discretion (e.g., for evaluation for pneumonia).

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 (blood pressure, respiratory rate, pulse rate and temperature) will be obtained in the sitting position. Patients should be sitting for 3-5 minutes prior to

obtaining vital signs. Weight will be taken at the start of each cycle while the patient is on Radium Ra 223 dichloride.

Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the calendar.

9.3.1 Interim Analysis for Safety

There will be no formal interim analysis of the efficacy data.

An interim analysis of the safety data will be conducted during the study. The interim analysis will be conducted when 10 subjects have completed treatment with 6 injections of radium-223 dichloride or discontinued study treatment early. The purpose of this interim analysis is to formally review safety data and to assess whether it is acceptable to continue enrollment of subjects. The review of the safety data in this interim analysis will be conducted by the HCI Data Safety Review Committee (DSMC). A proportion of subjects with grade 3 or higher hematologic adverse events significantly more than those reported for the radium-223 arm of the Phase 3 trial would be evidence of unacceptable toxicity. In particular, four or more grade 3+ anemias, three or more grade 3+ thrombocytopenias, or three or more grade 3+ neutropenias in ten subjects would be statistically significantly higher than expected (at the one-sided 0.05 significance level).¹⁹ An adjustment may be made to these numbers if the proportion of patients with prior chemotherapy is higher than the 59% reported in Parker et al (2013).¹⁹

A final safety analysis will be conducted when all 35 evaluable subjects have completed 6 doses of treatment, plus the end of treatment visit (30 days post-last dose), or discontinued treatment early.

9.4 Efficacy

9.4.1 Pre-study Documentation of Progressive Disease

Patients must have documented PD either by radiographic or PSA criteria as defined in Inclusion Criterion # 5.1.6 in Section 5.1.

Both radiographic PD and PSA PD must be assessed to evaluate eligibility; however, only one criterion (radiographic PD or PSA PD) must be met for Inclusion Criterion # 5.

PSA will be assessed at time points shown in the Schedules of Events.

Scans (CT/MRI) of the abdomen and pelvis and radionuclide bone scans will be used to monitor and assess disease response and progression, as described in the Schedule of Events. CT imaging of the chest is only required at baseline if clinically indicated. If disease is found in the chest, lesions should be followed by CT scan. The imaging modality for each patient must remain constant throughout the study. Additional scans should be performed at the

investigator's discretion if progression is suspected or to confirm the existence of bone lesions.

During the protocol specified treatment, disease progression will be defined per PCWG2 progression criteria. After completion of protocol defined therapy, the progression will be defined per clinical discretion of the treating clinician. Patients who complete study treatment without documented disease progression will continue to be followed by scans and PSA per the follow-up outlined in the study calendar until progression is seen or new treatment is started. All patients, regardless of date of progression, will be followed for 2 years post study enrollment for overall survival.

9.4.2 Radiographic Disease Assessment According to Prostate Cancer Clinical Trials Working Group (PCWG2) and Modified Response Criteria in Solid Tumors (RECIST Version 1.1)

Radiographic Disease Assessment will be performed using the PCWG2 guidelines. The PCWG2 recommends that for soft tissue lesions RECIST 1.1 assessment be applied and that results be compiled separately from the overall disease assessment, which includes both bone scan and RECIST 1.1 results.

Under RECIST 1.1, radionuclide bone scan lesions are considered not measurable, and hence nontarget. Under RECIST, bone scan progression occurs when the changes are "unequivocal." Under PCWG2, however, radionuclide bone scan results are treated semi-quantitatively and occurrence of new lesions may define progression as outlined further below. For this protocol, soft tissue and bone scan disease are evaluated separately, and the results of each are then considered in an overall radiographic disease assessment.

9.4.3 Recording Baseline Assessments

All sites of disease, target and nontarget lesions must be assessed at baseline. Patients with visceral metastases will be excluded from the protocol. Objective disease status is to be recorded at each evaluation using the response categories and definitions provided in this section.

9.4.4 Soft Tissue Lesion Assessment

Selection of Target and Nontarget Lesions

Selection of a Lymph Node as a Target Lesion

Only lymph nodes with a longest diameter ≥ 2 cm and a minimum short axis diameter ≥ 1.5 cm by CT scan will be considered as target lesions at baseline. All other lesions may be considered as nontarget, and are to be identified but not specifically measured at baseline, with the exception of bone scan metastases, which are identified and enumerated.

9.4.5 Response Definitions for RECIST-Evaluable Soft Tissue Lesions

9.4.5.1 Definition of Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.

9.4.5.2 Definition of Partial Response (PR)

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of longest diameters of non-lymph node lesions and of the short diameter(s) or short axis (SA) of lymph nodes.

9.4.5.3 Definition of Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

9.4.5.4 Definition of Soft Tissue Progression

At least a 20% increase in the sum of longest diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of 1 or more new measurable lesions is also considered progression.

9.4.5.5 Assessment of Soft Tissue Time Point Response

The following table summarizes the RECIST 1.1 response status calculation at each time point for patients who have measurable soft tissue disease at baseline. Note that this assessment does not include bone scan assessment and is not the overall assessment of radiographic disease status.

Table 8: Time Point Response: Patients with Target (± Nontarget) Disease

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR

SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

9.4.6 Radionuclide Bone Scan Assessment

9.4.6.1 Assessment

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

9.4.6.2 Post baseline Assessments and Definition of Progression of Bone Metastatic 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, ie, 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.

9.4.7 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.

Table 9: Overall Assessment Time Point Response

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

9.4.8 Progression Free Survival

Progression Free Survival by prostate-specific antigen (PSA) will be assessed for each patient on this study. Time to PSA progression is the time from the date of the first study drug administration to the first date that PSA progression is observed, according to the definitions below. Patients will have their PSA levels measured monthly while on study treatment. After the end of treatment visits, PSA assessments should be performed every 4-6 weeks visit until disease progression, or the start of another treatment.

Definition of PSA response:

- $\geq 30\%$ reduction of the blood level, compared to the baseline value.
- $\geq 50\%$ reduction of the blood level, compared to the baseline value.
- $\geq 90\%$ reduction of the blood level, compared to the baseline value.
- Confirmed PSA response: $\geq 50\%$ reduction of the blood level, compared to the baseline value, confirmed by a second PSA value approximately 4 or more weeks later.

Definition of PSA Progression:

- In patients with no PSA decline from baseline; $\geq 25\%$ increase from baseline value and an increase in absolute value of ≥ 2 ng/mL, at least 12 weeks from baseline.
- In patients with initial PSA decline from baseline; the PSA increase that is $\geq 25\%$ and at least 2 ng/mL above the nadir value, which is confirmed by a second value obtained three or more weeks later.

Changes and time to progression in total-ALP:

- Total-ALP response and progression; defined as for PSA above.

10 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

General considerations

Statistical analyses will be performed using Statistical Analysis Software®; the version to be used will be specified in the SAP.

Determination of sample size of the randomized cohort

Serum N-telopeptides levels are inversely associated with overall survival, based on data from the SWOG 0421 trial. The primary endpoint for statistical analysis for this study will be a comparison of the change in N-telopeptides from baseline to EOT or at disease progression (whichever comes earlier) between the randomization groups. The change in log 2 N-telopeptides will be compared to the change in a control group treated with enzalutamide alone using an ANCOVA model with the final value as response, treatment group as predictor and initial log 2 N-telopeptides as an adjustment variable. Based on the data from the SWOG 0421 study, the estimated baseline mean and standard deviation of log2 N-telopeptides are 3.95 nM and 1.14 nM respectively. We further assume the Pearson correlation of baseline and follow up N-telopeptides is 0.50. With these assumptions, and with 27 evaluable patients in the radium-223 + enzalutamide arm and 12 evaluable patients in the enzalutamide only arm there will be 85% power to detect a difference of 1.14 in the change in log 2 N-telopeptides between treatment arms using a two-sample t-test at the two-sided 0.05 significance level.

Randomization

A total of 39 patients will be randomized, 27 patients to the enzalutamide + radium-223 arm and 12 patients to the control enzalutamide only arm. The Research Compliance Office will randomize patients and maintain the randomization table for this trial.

Analysis sets

The *safety population*, which includes all subjects who receive at least one dose of study drug, will be used for the safety analysis.

The *randomized population*, which includes randomized subjects with follow up to EOT or disease progression (whichever comes earlier) will be used for the primary efficacy analysis. This population *excludes* patients enrolled prior to randomization.

The *combined population* includes all subjects treated with enzalutamide + radium-223 or enzalutamide alone with follow up to EOT or disease progression (whichever comes earlier). This population includes subjects enrolled prior to randomization with sufficient follow up. The combined population will be used for secondary and exploratory analyses.

10.1 Primary Endpoint Analyses

The co-primary endpoints are efficacy, safety and feasibility:

1. The primary efficacy endpoint is the change in serum N-telopeptides from baseline to end of treatment or progression (whichever comes earlier).
2. The primary safety endpoint is grade 3 or higher non hematological adverse events. The safety population will be used for all safety analyses. Safety analyses will be stratified by treatment arm.

10.1.1 Primary Bone Marker Analysis

Concomitant treatment with radium-223 (a bone targeting agent) and enzalutamide (a tumoricidal agent) is expected to decrease the level of N-telopeptides. As mentioned in the Background Section, serum N-telopeptides levels are inversely associated with overall survival, based on data from the SWOG 0421 trial. The primary endpoint for statistical analysis for this study will be the change in log 2 N-telopeptides from baseline to EOT or at disease progression (whichever comes earlier) between the randomization groups. If a bone marker test is missed at a given time point, every effort will be made to obtain the bone marker levels as early as possible. If two subsequent bone marker tests are missed, the patient will be excluded from the analysis. Equality of the change in log2 N-telopeptides between the treatment arms will be tested using an ANCOVA model with treatment group as the primary predictor and initial log 2 N-telopeptides as adjustment variable.

As a sensitivity analysis an F-test for equality of variance of final log2 N telopeptides will be performed. If the null hypothesis is rejected at the 0.1 significance level an additional ANCOVA model allowing for unequal variances will be fit.

10.1.2 Additional Analyses of the Primary Endpoint

Separate analyses in the combined population will be performed in subjects treated with enzalutamide + radium-223 and subjects treated with enzalutamide alone. If a bone marker test is missed at a given time point, every effort will be made to obtain the bone marker levels as early as possible. If two subsequent bone marker tests are missed, patient will be excluded from the analysis.

Based on the data from the SWOG 0421 study, the estimated baseline mean and standard deviation of log2 N-telopeptides are 3.95 nM and 1.14 nM respectively. We further assume the Pearson correlation of baseline and follow up N-telopeptides is 0.50. With 35 evaluable subjects there will be 80% power to detect a change of 0.556 in log2 N-telopeptides using a paired t-test. Extrapolating from SWOG0421, a decrease of 0.556 in log2 N-telopeptide concentration would translate into an approximate 20% increase in median overall survival.

10.1.3 Primary Safety Analyses

An overall proportion of subjects with grade 3 or higher hematologic adverse events significantly higher than those reported for the radium-223 arm of

Parker et al. (2013) would be evidence of unacceptable toxicity.^{8,19} The sum of the proportion of subjects in Parker et al. (2013) with grade 3+ anemia, thrombocytopenia, or neutropenia is 21%. An exact binomial test will be performed at the one sided 0.05 significance level comparing the proportion of subjects with one or more of grade 3+ anemia, thrombocytopenia, or neutropenia to 21%. With a safety population of 35 evaluable patients, 13 or more patients with one or more of grade 3+ anemia, grade 3+ thrombocytopenia, or grade 3+ neutropenia would indicate an unacceptable hematologic adverse event rate.

Exact 90% confidence intervals will be calculated for adverse events and serious AEs. With 35 evaluable patients an exact 90% confidence interval for an AE will extend no more than 17.5% from the observed proportion, and there is a 90% probability that an adverse event with a probability of 6.4% will be observed at least once.

10.2 Secondary Endpoint Analyses

All other statistical analyses will be descriptive in nature. Exploratory comparisons may be made between treatment arms of the randomized population. For all analyses of the combined population each treatment arm will be analyzed separately. In general, summary statistics (n, mean, standard deviation, median, minimum, and maximum for continuous variables, and number of subjects and percentage in each category for categorical variables) will be provided. Time to event variables will be summarized using Kaplan-Meier curves, and their medians will be estimated using the Kaplan-Meier method.

Additionally, source data for summaries will be presented as subject data listings. The details for analyses will be specified in the SAP.

Secondary and Exploratory Variables

The exploratory variables include:

- rPFS
- Time to radiological bone progression
- Total ALP response rate
- Time to total ALP progression
- Percentage change in total ALP
- PSA response rate
- Time to PSA progression
- Time to first skeletal related event (as defined below)
- OS for 2 years after enrollment
- Percent change in opioid requirement (in morphine equivalent) during protocol treatment.

Skeletal related events include the following:

- Time to occurrence of first use of external beam radiotherapy to relieve skeletal symptoms
- Time to occurrence of first tumor related orthopedic surgical intervention
- Time to occurrence of first spinal cord compression
- Time to occurrence of first new symptomatic pathological bone fractures (vertebral and non-vertebral)

10.3 Exploratory Analyses

Exploratory analyses will be performed on the combined population. For additional exploratory purposes, Kaplan-Meier curves and estimates will be presented for time to event variables (rPFS, time to radiological bone progression, time to total ALP progression, time to PSA progression, OS, time to first SRE).

Frequencies and percentages will be provided for categorical variables (total ALP response rate, PSA response rate, pain response rate). Summary statistics (n, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables (percentage change in total ALP).

Further details, including handling missing data and additional censoring details, will be described in the SAP.

11 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 fourteen days after registration. The date of registration will be the date of enrollment.

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

Treatment to Enzalutamide and Radium or Enzalutamide alone will be assigned at the time of enrollment. A randomization code will be created by a biostatistician and given to the Research Compliance Office to maintain and assign treatment to each patient as they are enrolled.

12 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. CRF's 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. Data capture will also include a form identifying which patients received bisphosphonates or denosumab prior to study entry. 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.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Informed consent

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

Each subject / legal representative or proxy consentor will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject / legal representative or proxy consentor voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject / legal representative or proxy consentor will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures.

If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of Bayer and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

The informed consent form and any other written information provided to subjects / legal representatives or proxy consentors will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed

consent form. Any revised written informed consent form and written information must receive the IEC/IRB's approval

13.2 Institutional Review

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

13.3 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).

13.4 Adverse Events / Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.03 for AE and SAE reporting. An electronic copy of the CTCAE Version 4.03 can be downloaded from:

<http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx>

The sponsor is responsible to comply with the local regulation and legislation for adverse events reporting.

All subjects who receive at least one dose of study treatment will be valid for the safety analysis.

All AEs whether considered drug-related or not, will be reported with a diagnosis, start/stop dates, action taken, whether treatment was discontinued, any corrective measures taken, outcome, and other possible causes. For all events, the relationship to treatment and the intensity of the event will be determined by the investigator.

Safety variables may include but not limited to the following: laboratory changes (complete blood counts, electrolytes, chemistry, and coagulation), changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature) and ECG and, in some instances, changes in chest x-ray images,

as produced at the investigator's discretion (e.g., for evaluation for pneumonia).

13.4.1 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.

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

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, 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 4.03 (grade 1-5).
2. its relationship to the study drug(s) (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 7 for guidance). Once an adverse event is detected, it should be followed until its resolution, 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.

Investigators should refer to the Safety Information section of the current IB for Ra 223 dichloride and the current IB for enzalutamide, including the DCSI

(development core safety information), for the expected side effects of Ra 223 dichloride. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions. The IB will be updated if any new relevant safety data are obtained.

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

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

13.4.2 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- 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

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

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 which 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.

13.5 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 as soon as possible, but no later than 10 days of first knowledge or notification of event (5 days for fatal or life threatening event).

The Medwatch 3500A form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf>

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 24 hours 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.

- For non-IND studies - The MedWatch report will be submitted to the FDA through the voluntary reporting method by the Regulatory Coordinator.

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:

- **All serious adverse events should be reported to Bayer within 24 hours of awareness of the event and must include the minimum information:**

1. The name and contact information of the reporter
2. The name of the study drug(s)
3. A description of the reported SAE
4. A patient identified by one or more of the following:
 - a. Patient initials
 - b. Patient number
 - c. Knowledge that a patient who experienced the adverse event exists
 - d. Age
 - e. Sex
5. An investigator assessment of study drug causality. For studies with combination therapy, a separate causality assessment should be provided for each study drug.

- Additional data which would aid the review and causality assessment of the case include but are not limited to:

The date of onset

The severity

The time from administration of study drug(s) to start of the event

The duration and outcome of the event

Any possible etiology for the event

The final diagnosis or syndrome, if known

- **All Medwatch 3500A reports shall be sent electronically to:**

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

Facsimile: (973) 709-2185

Address: Global Pharmacovigilance - USA

Mail only Bayer HealthCare
 P.O. Box 915
 Whippany, NJ 07981-0915
Address: 100 Bayer Blvd., Whippany, NJ 07981
FDX or UPS only: 67 Whippany Road, Whippany NJ 07981

Reports for all Bayer products can also be phoned in via our
Medical Communications Department:

Phone: 1-888-842-2937

**The Principal Investigator commits to respond promptly to
any query from Bayer regarding SAE reports.**

13.6 Pregnancies

The investigator must report to Bayer any pregnancy occurring in a study subject's partner during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used.

13.7 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.

13.8 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 meet any of the following criteria:

- Exceptions to eligibility criteria.

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

13.9 FDA Annual Reporting

This study is IND exempt therefore there are no annual reporting requirements to the FDA.

13.10 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.

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