The CUSP Group, LLC
A Uro-Oncology Trial Management Organization

ESCALATE, A Phase III Randomized Study Comparing Enzalutamide or Darolutamide with Radium-223 vs Enzalutamide or Darolutamide with Placebo and the Effect upon Symptomatic Skeletal Event-Free Survival for mCRPC Patients

STUDY NUMBER:	PC18-1005
STUDY DRUG(S):	Radium-223, Darolutamide, Enzalutamide
SPONSOR/CRO:	MANA RBM 1401 Wewatta St. Unit 813 Denver, CO 80202 pmanasco@manarbm.com
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VERSION	1.2
DATE FINAL:	04 MAY 2020

ESCALATE, A Phase III Randomized Study Comparing Enzalutamide or Darolutamide with Radium-223 vs Enzalutamide or Darolutamide with Placebo and the Effect upon Symptomatic Skeletal Event-Free Survival for mCRPC Patients

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Lead-Principal, Study Co-Principal and/or Site Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance with the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

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Trials Management Organization Thomas Paivanas, MHSA The CUSP Group, LLC/ CUSP Clinical Research Consortium	Trials Management Organization Signature	Date

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By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

Site Principal Investigator Name (Please Print)	**Site Principal Investigator Signature**	**Date**

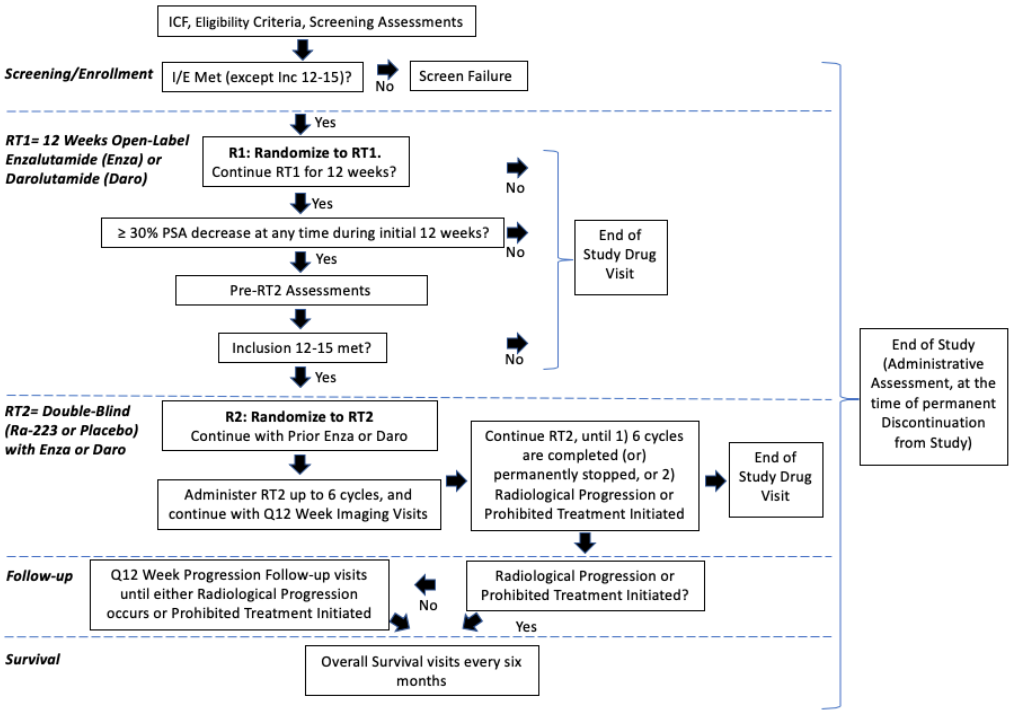
Protocol Amendment Changes

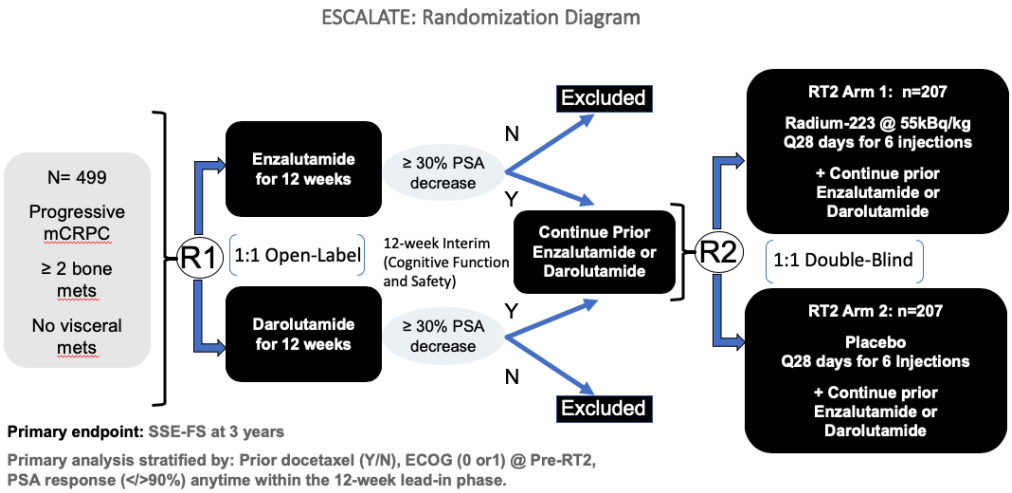
Protocol Version	Changes Made	Sections Affected
1.1	Redundant Schedule of Assessments removed	Section 8.2: Schedule of Assessments removed.
1.1	Addition of footnotes ab and ac.	Appendix C
1.1	Added PCWG3 expectations for Screening and RECIST/PCWG3 expectations for Pre-R2 visit.	Sections 10.2 and 10.4
1.1	Revised Inclusion #13	Inc/Exc: pages 13 and 34.
1.1	Moved Abbrev. PE from Q12Week imaging to Cycle 4, Day 1 only.	Schedule of Assessments Appendix C. Sections 10.5 and 10.6.
1.2	Added estimated creatinine clearance >/= 30 mL/min by Cockroft-Gault calculation to inclusion 9.	Synopsis and 3.1 Inclusion Criteria
1.2	Added specific details from full prescribing information for (Xofigo, Xtandi, and Nubeqa) regarding allowed dose modifications and special precautions.	Section 9- Dose Modifications
1.2	Added language to allow remote and telemedicine visits: “Visits may be split over multiple days if needed and may be conducted via remote visits (non-clinic) or via telemedicine visits as needed to facilitate visit completion and infection control (e.g. limit COVID-19 exposure).”	Section 10.1

1.2	Removed TUG at screening. It is only needed at Lead-in RT1 Day 1 (prior to RT1 first dose).	Section 10.2
1.2	Updated Enza compliance to: "Enzalutamide or Darolutamide Estimated Compliance (RT1 Days 28, 56, and 84 only)"	Section 10.3
1.2	Updated Enza compliance to: "Enzalutamide or Darolutamide Estimated Compliance"	Section 10.4
1.2	Updated Enza compliance to: "Enzalutamide or Darolutamide Estimated Compliance"	Section 10.5
1.2	Updated Enza compliance to: "Enzalutamide or Darolutamide Estimated Compliance"	Section 10.8
1.2	Updated Enza compliance to: "Enzalutamide or Darolutamide Estimated Compliance"	Section 10.9
1.2	Added sentence providing more detail on safety interim analysis	Section 13.6.1

PROTOCOL SYNOPSIS

Title of Study:	ESCALATE, A Phase III Randomized Study Comparing Enzalutamide or Darolutamide with Radium-223 vs Enzalutamide or Darolutamide with Placebo and the Effect upon Symptomatic Skeletal Event-Free Survival for mCRPC Patients	
Study Number:	PC18-1005	
Sponsor:	MANA RBM	
Study Duration:	The total duration of the study is 50 months: 18 months recruitment, 30 months follow-up, and a 2 month close-out period.	**Phase of Study:** III
Study Centers:	This study will be conducted at approximately 20 sites	
Number of Patients:	Approximately 499 patients are planned to be randomized 1:1 to open-label enzalutamide or darolutamide (Randomization #1 [R1]; Randomized Treatment #1, [RT1]) and approximately 414 of these patients will be subsequently randomized 1:1 to double-blind radium-223 or placebo (Randomization #2 [R2]; Randomized Treatment #2, [RT2]) while continuing enzalutamide or darolutamide androgen receptor blocker (ARB) therapy.	
Objectives:	**Primary Objective** The primary objective of this study is to: • To compare the symptomatic skeletal event-free survival (SSE-FS) of patients on radium-223 vs. placebo while taking randomized ARB therapy. **Secondary Objectives** The secondary objectives of this study are to: • Assess overall survival (OS) • Assess time to chemotherapy initiation after RT2 Cycle 1, Day 1 (C1D1) • Assess radiographic progression-free survival (rPFS) after RT2 C1D1 • Determine the safety profile of androgen receptor blocker (ARB) therapy with or without radium-223 • Assess occurrence of AESI: bone fractures (pathologic and non-pathologic) **Exploratory Objectives** The exploratory objectives of this study are to: • Compare the safety and cognitive function of enzalutamide and darolutamide from RT1 randomization through 12 weeks of enzalutamide or darolutamide (prior to RT2)	

	• Determine skeletal progression using PCWG3 criteria for progression based upon 99Tc bone scan imaging after RT2 randomization • Determine the time to PSA progression following RT2 randomization • Determine the total alkaline phosphatase (ALP) response rate every 12 weeks following RT2 randomization • Assess time to total ALP progression • Assess time to lactate dehydrogenase (LDH) progression • Assess further correlative biomarkers in the patient population • Assess frequency of the following adverse events that are listed as warnings for the study drugs (cardiovascular, seizures, falls, weakness, cognitive function)
Study Schema:	

Randomization to Treatments	
Study Design:	This is a randomized, multi-center, Phase III, double-blind, placebo-controlled study in patients with mCRPC. **Screening** Patients will be screened -42 to -2 days prior to starting RT1 treatment with an androgen receptor blocker (ARB). **R1** Following successful screening for first randomization (i.e., R1 I/E are met), patients will be randomized (R1) 1:1 to open-label randomized treatment 1 (RT1) with one of ARB's: enzalutamide or darolutamide. Patients may not switch RT1 ARB treatment during the study. **RT1:** ***Day 1, Day 28, Day 56 and Day 84*** Ensure patient is taking bone health agent (BHA) at or before first RT1 dose and continues on BHA throughout RT1 and RT2 treatment periods. Patients must receive at least 12 weeks of RT1 prior to Pre-R2 visit and before starting randomized, double-blinded Ra-223 or placebo (RT2). Patients will have serial PSAs performed at least every 4 weeks during the first 12 weeks of RT1 therapy.

Pre-R2

Pre-R2 baseline assessments will be done after 12-16 weeks of RT1 have been completed and no less than 14 days prior to RT2 (C1D1) to review safety parameters and establish baseline values prior to C1D1. ***Imaging assessments (CT, MRI, Bone Scan) should only be done for patients that have a documented ≥ 30% PSA decline at any time during the first 12 weeks of RT1.***

Subjects must meet additional inclusion criteria 12-15 in order to be qualified for the second randomization (R2). Only subjects that complete the initial 12 weeks of run-in RT1 should be evaluated for the additional inclusion criteria. Prior inclusion criteria 1-11 do not need to be re-evaluated. ***All subjects that complete the lead-in RT1 treatment should perform the second series of Cognitive function testing, even if they do not qualify for R2, prior to discontinuation.***

R2

If the all (R2) randomization conditions are all met, subjects will be eligible for (R2) randomization and should start the 1st cycle of (RT2) Ra-223 or placebo (C1D1) within 14 days following the pre-R2 safety laboratory blood draw.

Patients eligible for RT2 will be centrally randomized in a 1:1 ratio to receive either radium-223 dichloride or placebo (saline) administered IV on Day 1 of each cycle for 6, 28-day cycles, and will continue with their open-label, randomized ARB and BHA throughout the RT2 treatment period. The placebo will be administered in precisely the same fashion as the active drug.

RT2, *up to 6 cycles:*

Randomized, Double-Blind Ra-223 or Placebo Cycles 1-6: q 28 days

First RT2 cycle (C1D1) must occur within 14 days after the pre-R2 safety laboratory blood draw. Ideally, subsequent RT2 cycles 2-6 should be scheduled to occur every 28 days +/- 7 days following the previous cycle, but dosing may be delayed up to 4 weeks per cycle (maximum 8 weeks between cycles). Patients will continue with their open-label, randomized ARB irrespective of Ra-223/placebo delays. Subjects should continue on BHA throughout the RT2 treatment period.

Safety laboratory assessments must be completed within 14 days of each cycle and results assessed for safety to proceed with next cycle before administration.

Q12-Week RT2 Imaging

After the first administration of RT2 at C1D1, patients will be assessed radiologically by CT or MRI and bone scan every 12 weeks, until either:

1) radiological progression defined as soft tissue progression per RECIST 1.1 or bone progression per PCWG3 or

2) a prohibited treatment has begun.

The 12-week visits start 12 weeks +/- 7 days after RT2 Cycle 1, Day 1 and must remain on this schedule independent of other study visits. The same imaging modality should be used for all assessments (CT or MRI). The RECIST and PCWG3 tumor assessments should be completed by the same trained rater throughout the study.

Telephone End of Study Drug(s)

Telephone End of Study Drug Visits are required 30 days +/- 7 days after last dose of study drug(s) (Ra-223/Placebo, Enzalutamide, and Darolutamide) are administered or at the last clinic visit if patient declines further participation.

Q12-Week Progression Follow-up

After RT2 cycles are either stopped or (6) cycles completed, patients without radiological progression that have not started a prohibited treatment will continue to have clinic visits every 12 weeks (continuing with the same schedule based on C1D1). Enzalutamide or Darolutamide may continue during the Q12-Week Progression Follow-up period. PSA progression alone is not considered progression in this protocol [Scher et al. 2016]. Clinical progression will be assessed by the site investigator on any scheduled or unscheduled visit.

Overall Survival

Patients that demonstrate radiological progression or start a prohibited treatment will be followed for SSE's, AESIs, and overall survival. Enzalutamide or Darolutamide may continue during the Overall Survival period. Patients in this phase of the study will be evaluated every 6 months +/- 1 month after the last Q12-Week Visit is performed until death or the end of the study. Patients may be contacted during outpatient visits or by telephone and/or chart review.

End of Study:

When patients permanently discontinue the study due to any reason (screen failure, lost to follow-up, withdrawn consent, etc.), an End of Study visit will be done to capture the reason for screen failure, reason for permanent discontinuation, study disposition, and to assess AEs.

Study Drugs, Doses, and Modes of Administration:	**Randomized Treatment #1, RT1** Ensure patient is taking a bone health agent (BHA) at the time of starting RT1. Patients eligible to receive RT1 will be randomized (R1) in a 1:1 ratio to receive open-label enzalutamide (160 mg PO QD) [available commercially through prescription] or darolutamide (600 mg PO BID) [provided through the study] for mCRPC. Dose reductions of RT1 will be allowed per protocol (see dose-reduction guidelines). Once receiving RT1, subjects should continue RT1 on study until toxicity, or other reason listed in section 3.4. Patients who do not have a ≥ 30% PSA decline at any time during the RT1 period will not be randomized to RT2 and will be discontinued from the study. Patients must receive RT1 at least 12 weeks and meet all R2 conditions to proceed to the second double-blind randomized treatment phase. **Randomized Treatment #2, RT2** Patients eligible to receive RT2 will be randomized (R2) in a 1:1 ratio to receive double-blind RT2 (radium-223 or placebo) that will be administered IV on Day 1 of each cycle for 6, 28-day cycles). RT2 active and placebo treatments will be administered in precisely the same fashion on Day 1 of each cycle for 6, 28-day cycles. Patients will continue with their open-label, randomized ARB and bone health agent. Randomized (Ra-223 or Placebo) will be blinded to patient and study staff /investigators who perform any study related procedures/tasks. Designated trained, unblinded individual or individuals will prepare and administer radium-223 at 55 kBq/kg IV or placebo via intravenous infusion on Day 1 of a 28-day cycle for a total of 6 cycles. No dose reductions will be allowed, but treatment can be held for up to 4 weeks. If the hold is the result of a treatment-related AE and lasts for >4 weeks, then treatment will be permanently discontinued. No less than 3 weeks and no more than 8 weeks is allowed between doses. Patients will be evaluated for toxicity within 14 days prior to each cycle. Radiological assessments will be performed every 12 weeks following Cycle 1 Day 1, as defined in Appendix C, page 94. Patients will continue on RT2 for up to 6 cycles or until patient has a reason for discontinuation as listed in Section 3.5 of the protocol. Upon radiographic progression, further treatments are decided by the site investigator according to standard local practice. Radium-223 or placebo may continue at the discretion of the site investigator (if the maximum of 6 doses have not been reached) if they believe it to be in the patient's best interest. If patient continues on Ra-223 or placebo after radiological progression, the Q12 Week Imaging visits will not be done, and the patient will move into Overall Survival phase after all Ra-223 or Placebo cycles are completed. Enzalutamide or

	darolutamide may be continued after progression if the treating investigator considers that the patient is still receiving benefit. PSA progression alone is not considered progression in this protocol [Scher et al. 201 Clinical progression will be assessed by the site investigator on any scheduled or unscheduled visit.

Inclusion Criteria:	Patients must meet all of the following inclusion criteria in order to be qualified for the first randomization (R1) to Open-label Enzalutamide or Darolutamide (Lead-in Phase): 1. Able and willing to provide informed consent. 2. Histologically or cytologically confirmed diagnosis of prostate adenocarcinoma. 3. Men ≥ 18 years. 4. ECOG performance status of 0 or 1 at screening. 5. Metastatic to bone with ≥ 2 bone metastases (area of increased uptake on ^{99m}Tc bone scan); equivocal lesions on the bone scan must be confirmed by standard X-ray, CT, or MRI. 6. Patients must have progressive metastatic castration-resistant prostate cancer (mCRPC) at screening and on androgen deprivation therapy (ADT) as evidenced by either: a. For patients who manifest disease progression solely as a rising prostate-specific antigen (PSA) level - documentation of a sequence of two rising PSA values at a minimum of 1-week apart with the Screening value ≥1 ng/ml (see Appendix D); b. For patients with disease progression manifested in the bone, irrespective of progression by rising PSA – defined by the appearance of 2 or more new skeletal lesions demonstrated by 99Tc bone imaging. Ambiguous results should be confirmed by other imaging modalities than bone scan and x-ray (e.g.: CT-scan or MRI). c. For patients with disease progression manifested at nodal sites, irrespective of progression by rising PSA - progression defined per RECIST 1.1. 7. Ongoing ADT with luteinizing hormone-releasing hormone (LHRH) agonist or antagonist or bilateral orchiectomy. 8. Use of bone health agents (denosumab or zoledronic acid or other bisphosphonates) starting any time prior to R1 unless contraindicated or considered not in the best interest of the patient. A waiver must be approved by the medical monitor if bone health

	agents cannot be used. Bone health agents should be continued throughout both RT1 and RT2 treatment periods. 9. Adequate bone marrow and organ function as defined by: a. Hemoglobin ≥ 10.0 g/dL b. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L c. Platelets ≥ 100 x 10^9/L d. Serum creatinine ≤ 1.95 mg/dL e. Estimated creatinine clearance >/= 30 mL/min/1.73m2 by Cockroft-Gault calculation f. Alanine aminotransferase (ALT) ≤ 175 U/L g. Aspartate aminotransferase (AST) ≤ 100 U/L h. Total bilirubin ≤ 1.8 mg/dL (unless the patient a diagnosis of Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin; in patients with Gilbert's, the total bilirubin should be less than 6 mg/dL if patient has Gilbert's and the elevation should be seen in the unconjugated or indirect bilirubin measurement) i. LDH ≤ 224 U/L at screening. j. Albumin ≥ 2.5 g/dL 10. Fertile male patients, defined as all males physiologically capable of conceiving offspring with female partners of child-bearing potential, must be willing to use condoms plus spermicidal agent during the study treatment period and for 6 months after the last dose of study drug, and not father a child or donate sperm during this period. 11. The treating site investigator deems RT1 (Enzalutamide or Darolutamide) treatment safe and feasible. Subjects must meet the remaining inclusion criteria in order to be qualified for the second randomization (R2). Only subjects that complete the initial 12 weeks of run-in RT1 should be evaluated. Prior inclusion criteria do not need to be re-evaluated: 12. Patients must have a documented ≥ 30% decline of PSA at any time during the 12 weeks of RT1. 13. Patients must have no evidence of visceral metastatic disease at the time of RT2 randomization. 14. Ongoing treatment with RT1 and bone health agents at time of RT2 randomization. 15. The treating site investigator deems RT2 (Ra-223 dichloride) treatment safe and feasible.
Exclusion Criteria:	Patients who meet any of the following criteria will be excluded from study entry: 1. Pathological finding consistent with small cell carcinoma of the prostate.

	2. Prior chemotherapy for CRPC. Prior docetaxel for hormone-sensitive disease is permitted under the following conditions: started within 3 months of ADT initiation, given for a maximum of 6 cycles and progression occurred > 6 months after the last dose of docetaxel. 3. Prior treatment for mCRPC or CRPC. However, the following therapies are permitted and not exclusionary: Sipuleucel-T, 5-alpha-reductase inhibitors, estrogens, or older antiandrogens (such as flutamide, bicalutamide, or nilutamide). 4. Prior treatment for more than 2 months with CYP17 inhibitors (e.g. abiraterone or orteronel). 5. Prior treatment for more than 2 months with agents inhibiting androgen receptor signaling (e.g. enzalutamide, apalutamide, or darolutamide). 6. Prior hemibody or whole-body external radiotherapy. Other types of prior external radiotherapy and brachytherapies are allowed. 7. Prior therapy with radionuclides (e.g., radium-223, strontium-89, samarium-153, rhenium-186, rhenium-188, actinium-225 and lutetium-177). 8. Current involvement in any drug or device trial involving investigational agent or medical device within the last 28 days prior to R1. 9. In general, any prior investigational agent for nmCRPC/mCRPC; however, may be reviewed by medical monitor/PIs for waiver consideration, on a case-by-case basis. 10. Hypersensitivity to compounds related to enzalutamide, darolutamide, or Ra-223. 11. A blood transfusion ≤ 28 days prior to R1. 12. Major surgical procedures ≤ 28 days or minor surgical procedures ≤7 days prior to R1. No waiting period is required following port-a-cath placement. 13. Patients with visceral metastases, clinical evidence of central nervous system metastases, or leptomeningeal tumor spread as demonstrated via CT/MRI of chest, abdomen, pelvis, and CNS (if needed). CT/MRI of the CNS only performed if suspicion of CNS metastases or leptomeningeal tumor spread. Nodules < 1 cm alone will not be considered visceral metastases. Renal masses < 3 cm will not be considered exclusionary. 14. Serious active infection at the time of screening or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment. 15. Presence of other active cancers, or history of treatment for invasive cancer ≤2 years of R1. Patients with Stage I/II cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) and superficial bladder cancer are eligible, as are patients with history of non-melanoma skin cancer. 16. Any other serious or unstable illness, or medical, social, or psychological condition, that could jeopardize the safety of the subject and/or his/her

	compliance with study procedures, or may interfere with the subject's participation in the study or evaluation of the study results."
Correlative Testing:	Optional blood samples (i.e., plasma and serum samples) will be collected from patients that provide consent. Samples will be collected at 3 timepoints: • Pre-RT1: Prior to enzalutamide or darolutamide dosing • Pre-R2: After 12-week Lead-in enzalutamide or darolutamide, and • Following confirmed radiographic progression or prior to initiation of a prohibited anti-cancer treatment, whichever occurs earlier Blood samples will be sent to a central biorepository. Samples may also be analyzed for exploratory biomarkers to evaluate predictive biomarkers and to assess correlation with disease activity, effects of study drug, and clinical outcomes.
Cognitive Testing and Patient Reported Outcomes	Cognitive Function testing (CANTAB battery of Cognitive Function Tests) and patient reported outcomes (FACT-P and FACT-Cog) will be done to determine changes that may occur during the study in relation to exposure to different treatments. Data collection will be done electronically at the following timepoints: • Screening (practice) • Lead-in RT1, • Pre-R2
Statistical Methodology:	The following stratification variables will be used in the RT2 randomization process: • PSA response (≥90% vs < 90% decline at any time from initiation of RT1) • ECOG Score 1 or 0 at Pre RT2 visit • Prior docetaxel use (yes vs no) The primary endpoint of this 1:1 randomized Phase III study is SSE-FS with the following assumptions: • The ERA-223 study (published data) suggests that the median SSE-FS rate for the placebo control arm is 24 months, as per the Bayer adjustment of -4 months. • HR = 0.70 • Median SSE-FS for enzalutamide of 34.3 months (under the exponential assumption). • Two-sided alpha = 0.05 • Power = 0.80 • Cumulative drop-out rate by the end of the study = 10%

We anticipate:

Power	Recruitment Period (months)	Follow-up Period (months)	Expected Number of Events	Total Number of Patients Randomized at R2
80%	18	32	246	414

No interim analysis for efficacy or futility is being planned. Fifty nine percent of randomized patients are expected to contribute with an event.

Descriptive statistics, including mean, median, standard deviations and ranges for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time-to-events endpoints will be reported using Kaplan-Meier estimates, with 95% CI for median time-to-event.

PC18-1005 CONTACT INFORMATION

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Trial Management Organization **CUSP Group/CUSP Clinical Research Consortium**	Thomas Paivanas, MHSA 4440 Sleaford Rd Annandale VA 22003 703-764-4984 Tom@cuspgroup.net

LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ARB	Androgen Receptor Blocker
AST	Aspartate aminotransferase
BCT	Blood Collection Tube
BHA	Bone Health Agents
BP	Blood pressure
Bq	Becquerel
BUN	Blood urea nitrogen
C1D1	Cycle 1, Day 1 of Ra-223 or Placebo
CBC	Complete blood count
CBR	Clinical benefit rate
CFR	Code of Federal Regulations
CI	Confidence interval
CMP	Comprehensive metabolic profile
CO_2	Carbon dioxide
CR	Complete response
CT	Computed tomography
CTC	Circulating Tumor Cells
ctDNA	Circulating Tumor DNA
DNA	Deoxyribonucleic Acid
ENZA	Enzalutamide
EBRT	External beam radiotherapy
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eICF	Electronic informed consent form
eISF	Electronic investigator site file
eTMF	Electronic trial master file
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HSPC	Hormone-sensitive prostate cancer
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee

LIST OF ABBREVIATIONS

IRB	Investigational review board
IV	Intravenous
LDH	Lactate dehydrogenate
LHRH	Luteinizing hormone-releasing hormone
mCRPC	Metastatic castration-resistant prostate cancer
MRI	Magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PCWG	Prostate Cancer Clinical Trials Working Group
PD	Progressive disease
PS	Performance Status
PHI	Protected health information
PR	Partial response
PSA	Prostate-specific antigen
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	Ribonucleic Acid
rPFS	Radiographic progression-free survival
R1	First Randomization- 1:1, Open-Label
RT1	Randomized Treatment #1 (Open-Label Darolutamide or Enzalutamide)
R2	Second Randomization- 1:1, Double-Blind
RT2	Randomized Treatment #2 (Double-Blind Ra-223 or Placebo)
SAE	Serious adverse event
SAR	Suspected adverse reaction
SD	Stable disease
SSE	Symptomatic skeletal event
SSE-FS	Symptomatic skeletal event free survival
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAE	Unexpected adverse event
UCP	Unequivocal clinical progression
ULN	Upper limit of normal
USPI	US package insert
WBC	White blood cell

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1. INTRODUCTION

1.1 Background

Prostate cancer is responsible for the deaths of over 300,000 men annually world-wide [Ferlay et al. 2015]. Recurrent and advanced stages of the disease are initially treated with suppression of testosterone production through either orchiectomy or androgen deprivation therapy (ADT). Despite low levels of circulating testosterone, the disease progresses and is termed castration-resistant prostate cancer (CRPC). The majority of CRPC patients have or will develop metastatic disease (mCRPC). Many patients with metastatic disease will experience clinically relevant events related to bone metastases, including pain, pathological fractures, and spinal cord compression. Since the regulatory approval of docetaxel chemotherapy in 2004 [Tannock et al. 2014], several life-prolonging treatments have become commercially available for mCRPC - including cabazitaxel, sipuleucel-t, radium-223, and novel androgen-targeted therapies (abiraterone acetate and enzalutamide)[Flaig et al. 2016). Despite the utilization of these drugs, increased benefit by early intensification in this setting has not been well established.

Enzalutamide:

Enzalutamide, a targeted androgen-receptor inhibitor that blocks binding of androgen to the androgen receptor, translocation to the nucleus, and DNA binding [Tran et al. 2009]. It has been FDA-approved for patients with mCRPC based on data from multiple phase III trials, including AFFIRM [Scher et al. 2012], PREVAIL [Beer et al. 2014], and TERRAIN [Shore et al. 2016], and approved for non-metastatic CRPC based on the PROSPER study [Hussain et al. 2018]. Enzalutamide demonstrated superiority to placebo for the treatment of mCRPC including median rPFS (20.0 vs. 5.4 months; hazard ratio 0.32, 95% CI: 0.28–0.37; $p < 0.0001$) and OS (35.3 vs. 31.3; hazard ratio 0.77, 95% CI 0.67–0.88; $p = 0.0002$) [Beer et al. 2017] in chemotherapy naïve patients and OS (18.4 vs. 13.6 months; hazard ratio 0.63; 95% CI: 0.53,0.75; $P<0.001$) in patients with prior chemotherapy exposure. The TERRIAN study further validated enzalutamide as a standard of care for mCRPC with a median progression-free survival of 15.7 months to 5.8 months in the bicalutamide arm (hazard ratio 0.44; 95% CI: 4.8, 8.1; $p<0.0001$).

Darolutamide:

Darolutamide, a novel androgen receptor antagonist, was approved for non-metastatic castration-resistant prostate cancer on July 30, 2019 based on the ARAMIS study (NCT02200614), a multicenter, double-blind, placebo-controlled clinical trial in 1,509 patients with non-metastatic castration resistant prostate cancer. Patients were randomized (2:1) to receive either 600 mg darolutamide orally twice daily (n=955) or matching placebo (n=554). All patients received a gonadotropin-releasing hormone (GnRH) analog concurrently or had a previous bilateral orchiectomy. Twelve patients with previous seizure histories were treated on the darolutamide arm.

The primary endpoint was metastasis free survival (MFS), defined as the time from randomization to first evidence of distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. The median MFS was 40.4 months (95% CI: 34.3, not reached) for patients treated with darolutamide compared with 18.4 months (95% CI: 15.5, 22.3) for those receiving placebo (hazard ratio 0.41; 95% CI: 0.34, 0.50; p<0.0001). OS data has yet to mature.

Alpha Particle-emitting therapy Radium-223

Radium-223 dichloride ([Radium-223], Xofigo®, Bayer Consumer Care AG) is an FDA approved alpha particle-emitting radioactive therapeutic agent indicated for the treatment of patients with CRPC, symptomatic bone metastases and no known visceral metastatic disease. Radium-223 mimics calcium and forms complexes with the bone mineral hydroxyapatite preferentially in areas of increased bone turnover, such as bone metastases. The high linear energy transfer of alpha particle emitters induces 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). This limited range of penetration depth minimizes damage to the surrounding normal tissue, including bone marrow, resulting in minimal myelosuppression. Radium-223 also acts by interrupting the vicious circle of interaction between the tumor microenvironment and the prostate cancer cells.

1.1.1 Clinical Studies with radium-223

The Phase I dose escalation study of radium-223 consisted of 25 breast and prostate cancer patients with osteoblastic lesions who were injected with a single dose of the agent. Pharmacokinetic studies demonstrated that within 24 hours, <1% of the administered dose remained in circulation and was predominantly eliminated via the gastrointestinal tract. Pain relief was reported by 52%, 60%, and 56% of patients after either 1, 4, or 8 weeks, respectively. 28% of patients experienced a “flare” phenomenon. There was a significant decline in alkaline phosphatase among the prostate patient cohort. No dose limiting toxicities (defined as platelets <20 x 109/L, or neutrophils <0.5 x 109/L) were experienced. Myelosuppression was mild and reversible with a nadir 2-4 weeks after drug administration. However, non-hematologic toxicity consisting of transient diarrhea (40% of patients), fatigue (25% of patients), and nausea or vomiting (20% of patients) occurred.

The Phase II double-blind, placebo-controlled trial randomized 64 men with CRPC to receive four intravenous (IV) injections of either 50 kBecquerel (Bq)/kg of radium-223 or placebo every 4 weeks. The primary endpoints were change in bone-alkaline phosphatase and time to skeletal-related events (SREs). At 4 weeks alkaline phosphatase levels were -65% in the radium-223 arm and +9.3% in the placebo arm (p<0.0001). Time to SREs was not statistically significantly different (14 versus 11 weeks, p=0.26). There was a statistically significant change in time to prostate-specific antigen (PSA) progression of 26 versus 8 weeks and a median change in relative PSA (-24% versus +45%). There was a trend to improvement in overall survival (OS) (65.3 versus 46.4 weeks, p=0.066), but the difference did not reach statistical significance.

Hematological toxicity was comparable in the two arms and noted only in the first 4 weeks of treatment with radium-223.

The Phase III placebo-controlled trial (ALSYMPCA) planned to randomize 921 men with symptomatic bone-metastatic CRPC in a 2:1 ratio to receive 6 injections at 4-week intervals of either radium-223 (50 kBq/kg) or placebo. Entry criteria included at least two metastatic bone lesions, no visceral metastases, and either prior docetaxel treatment or inability to receive docetaxel. The primary endpoint was OS, with secondary endpoints of time to first SSE, time to alkaline phosphatase progression, alkaline-phosphatase response, alkaline-phosphatase normalization, time-to-PSA-progression, safety endpoints, and quality-of-life. The study was designed with 90% power to detect a hazard ratio (HR) for death of 0.76 at 5% significance level. The two arms were well balanced in terms of baseline demographics. The trial was halted at an interim analysis after 809 patients had been randomized (541 on radium-223 and 268 on placebo) based on the fact that the OS for patients on the radium-223 arm was significantly longer than for patients on the placebo arm. At the planned interim analysis, 63% of the patients receiving radium-223 had received all 6 injections in comparison to 47% in the placebo arm. Median survival was significantly increased from 11.2 months to 14.0 months with a HR of 0.695 (p= 0.00185) in favor of radium-223. In the final analysis, radium-223 prolonged median OS compared with placebo, irrespective of previous docetaxel use (previous docetaxel use, HR 0.70, 95% confidence interval [CI] 0.56-0.88; p=0.002; no previous docetaxel use, HR 0.69, 0.52-0.92; p=0.01). Furthermore, radium-223 significantly prolonged the median time to first SSE compared to placebo (15.6 months vs. 9.8 months; hazard ratio, 0.66; 95% CI, 0.52 to 0.83; P<0.001) and demonstrated favorable ALP outcomes, including time in total ALP increase (hazard ratio, 0.17; 95% CI, 0.13 to 0.22; P<0.001), ALP response (P<0.001), and ALP normalization (P<0.001).

1.1.2 **Clinical Safety Summary**

Enzalutamide

Enzalutamide carries the following warnings and precautions in the US prescribing information:

* Seizures occurred in 0.4% of patients taking enzalutamide in clinical studies. In patients predisposed to seizures, 2.2% of patients taking enzalutamide experienced a seizure.

* Posterior Reversible Encephalopathy Syndrome was reported in post-approval use. Symptoms included seizure, headache, lethargy, confusion, blindness and other visual and neurology disturbances.

* Hypersensitivity reactions including edema of the face occurred in 0.5% of patients treated with enzalutamide in clinical trials.

* Ischemic Heart Disease was reported in 2.7% of patients treated 1.2% of patients on placebo.

* Falls and Fractures occurred in 10% of patients treated with enzalutamide compared to 4% of patients treated with placebo.

The most common adverse events, occurring in more than 10% of patients and >/= 2% over placebo included asthenia/fatigue, decreased appetite, hot flush, arthralgia, dizziness/vertigo, hypertension, headache and weight loss.

Drug interactions with CYP2C8 inhibitors (increase enzalutamide concentrations) and CYP3A4 inducers (decrease enzalutamide concentrations) were reported in the Package Insert. In addition, recommendations to avoid CYP3A4, CYP 2C9, and CYP2C19 substrates with narrow therapeutic indices (e.g. warfarin).

Darolutamide

The most common adverse reactions (≥2%) in patients who received darolutamide were fatigue, pain in extremity, and rash. Ischemic heart disease (4.0%) and heart failure (2.1%) were more common on the darolutamide arm.

The most frequent adverse events that required dose-interruptions were hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).

The most frequent adverse events that required dose-reductions were fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

The most frequent adverse events requiring permanent treatment discontinuation were cardiac failure (0.4%) and death (0.4%).

The most common laboratory abnormalities (all grades) were neutrophil count decreased (20%), AST increased (23%) and bilirubin increased (16%).

Radium-223

Warnings reported in the US package insert include the following:

* Bone Marrow Suppression- 2% of patients taking Radium-223 experienced bone marrow failure or ongoing pancytopenia

* Hematologic evaluation prior to treatment. Prior to first treatment the absolute neutrophil count should be >1.5x10^9/L, platelets should be >=100x10^9/L and hemoglobin >=10g/dL. Prior to subsequent doses, the ANC should be >=1x10^9/L and platelets >=50x10^9/L.

* Concomitant use with chemotherapy: the safety and efficacy has not been established

* Increased fractures and mortality in combination with abiraterone plus prednisone/prednisolone (discussed in section 1.2)

* Administration and radiation protection. Administration of Radium-223 is associated with potential risks to other persons from radiation or contamination from spills of bodily fluids.

* Fluid status-dehydration occurred in 3% of patients taking Radium-223 and 1% of placebo-treated patients

* Injection site reactions: erythema, pain and edema at the injection site occurred in 1% of patients taking Radium-223

Adverse events (AEs) have been assessed for any man who received ≥ 1 injection of radium-223. There were 762 patients in the safety assessment population in studies of radium-223. AEs were observed in 88% of the radium-223 patients and 94% of placebo-treated patients. Serious adverse events (SAEs) were higher in the placebo group (43% versus 55%) and treatment discontinuation due to AEs was higher in the placebo group (13% versus 20%). Grade 3/4 hematologic toxicities were comparable between the two arms: neutropenia (3% versus 1%), thrombocytopenia (6% versus 2%), anemia (13% versus 13%). Non-hematologic grade 3/4 toxicities included bone pain (21% versus 26%), nausea (2% in either cohort), diarrhea (2% in either cohort), vomiting (2% in either cohort), fatigue (5% versus 6%), and bone pain (21% versus 26%). A statistically higher percentage of patients had meaningful improvement in quality of life with radium-223 over placebo.

1.2 Radium-223 in combination with other therapies

The ALSYMPCA study showed that the addition of radium-223 to the best standard of care, including local external-beam radiation therapy (EBRT), treatment with glucocorticoids, antiandrogens, ketoconazole, or estrogens, extended OS compared to patients receiving standard of care plus placebo [Parker et al. 2013]. Notably, enzalutamide or abiraterone plus corticosteroid were not included in the study. Data from the expanded access program in Europe suggested that patients receiving concomitant radium-223 and enzalutamide or abiraterone plus corticosteroid lived longer than those individuals without such concomitant therapy [Jim et al. 2010]. This is further strengthened by data from the radium-223 US expanded access programs.

A combination trial of abiraterone plus prednisone/prednisolone in concurrent combination with radium-223 (ERA-223) reported results in 2018. This randomized double-blind, placebo-controlled Phase III ERA-223 trial investigated whether administering radium-223 dichloride (radium-223) in combination with abiraterone acetate plus prednisone/prednisolone increased symptomatic skeletal event free survival (SSE-FS). The trial has enrolled 806 patients who are randomized in a 1:1 ratio to receive study treatment (either radium-223 dichloride or placebo in addition to abiraterone acetate plus prednisone/prednisolone for the first six cycles followed by abiraterone acetate plus prednisone/prednisolone thereafter) until an on-study symptomatic skeletal event (SSE) occurs (or other withdrawal criteria are met). The study completed enrollment in September 2016. On November 14th, 2017, an Independent Data Monitoring Committee (IDMC) recommended to unblind the Phase ERA223 III trial due to the observation of an imbalance concerning more fractures and deaths events in the treatment arm investigating radium-223 in combination with abiraterone acetate and prednisone/prednisolone. In November

2017, Bayer had informed health authorities worldwide as well as investigators and healthcare professionals about the preliminary findings of an increased incidence of fractures and death in the Phase III ERA-223 study. Of note, only 39% and 42% of subjects received concurrent denosumab or bisphosphonate treatment in the radium-223 and placebo arms, respectively (Smith at al. 2019).

The FDA finalized its assessment of the Phase III ERA-223 trial results in August 2018 and the indication remains unchanged - Xofigo is indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. As a consequence of the results of the ERA-223 trial there was an update in the SmPC concerning Warnings and Precautions - Increased Fractures and Mortality in Combination with Abiraterone plus Prednisone/Prednisolone: Xofigo is not recommended in combination with abiraterone acetate plus prednisone/prednisolone.

Currently, the PEACE III study (NCT02194842) is ongoing and designed to answer the question of whether radium-223 in addition to enzalutamide improves radiological progression-free survival in patients with asymptomatic or mildly symptomatic mCRPC. This study initiates radium-223 and enzalutamide concurrently and does not address the optimal timing of radium-223. Following the unblinding of ERA-223, the PEACE III study was amended to mandate bone protective agents, either denosumab or zoledronic acid [Tombal et al. 2019]. subsequently published that subjects initiating bone protective agents at least 6 weeks before their first injection of radium-223 had significantly lower rates of bone fractures, regardless of the use of Ra-223. Of the subjects receiving enzalutamide and radium-223, 13 of 39 (33%) without a bone protective agent reported a fracture, while only 1 of 33 (3%) on a bone protective agent reported a fracture. There was no difference in the rate of fractures between enzalutamide and radium-223 in patients that received a bone protective agent; however, the number of patients evaluated was low.

1.3 The response of bone metastases to enzalutamide

Patients responding to enzalutamide therapy often have bone lesions that exhibit the bone flare phenomenon on a bone scan [Ryan et al. 2011]. The flare phenomenon is captured on bone scan as increased deposition within the hydroxyapatite associated with healing bone and represents an osteosclerotic reaction, with deposition of hydroxyapatite and presumably diminution of tumor size. Within the bone, there is an increase in elements to which radium-223 binds, while at the same time bone metastases are decreasing in size. This enhanced stromal/tumor ratio in bone is theoretically ideal for radium-223 therapy. This hypothesis has not been examined in preclinical or clinical studies.

1.4 Rationale for the Study

Thousands of patients with bone predominant mCRPC experience disease progression after an initial response to enzalutamide or abiraterone acetate and the next treatment choice is unclear due to the availability of multiple therapies. Clinical and disease characteristics often dictate and/or limit potential options. No randomized controlled studies have suggested one therapy

might be preferable to another in this setting or have established the ideal timing of radium-223, a novel radiopharmaceutical targeting bone metastases.

The optimal time to add radium-223 to an active hormone treatment regimen such as enzalutamide or darolutamide has not been well established. Recent data from ERA-223, a trial adding concomitant radium-223 or placebo to abiraterone acetate, demonstrated an increased risk of fractures in the radium-223 group [Smith et al. 2019]. The fracture risk was dramatically reduced when bone-protective agents were used. A post-hoc analysis showed that both groups of patients with alkaline phosphatase flares during the study had a lower proportion of fractures, compared to those without flares [Smith et al. 2019]. The ongoing PEACE-III study is investigating concurrent enzalutamide and radium-223 and only mandated bone health agents subsequent to the release of the ERA-223 fracture data.

The hypothesis we are testing in this study is whether layering radium-223 following 16 weeks of enzalutamide or darolutamide exposure in patients demonstrating a biochemical response improves disease outcomes. By adding radium-223 following a potential bone flare phenomenon (first 12-14 weeks of therapy with an androgen receptor blocker), maximizing patients expected to have durable response to systemic therapy, and using bone protective agents during treatment, we aim to demonstrate an optimal time to add radium-223 in the mCRPC landscape.

In this study, the efficacy of adding radium-223 after an initial PSA decline ≥30% at any time during a 12-week lead-in period of enzalutamide or darolutamide, will be assessed via time to symptomatic skeletal event-free survival (SSE-FS). In the PREVAIL study, the prognostic importance of PSA response was demonstrated; subjects experiencing an initial PSA response during enzalutamide treatment had better outcomes than those that did not, including time to PSA progression, rPFS, and overall survival. (Armstrong et al. 2018). As radium-223 targets the bone only, this study will select for patients that demonstrate systemic control of their disease (i.e. a biochemical response during oral therapy) to enable higher likelihood of patient benefit. SSE-FS is a clinically meaningful endpoint defined as the first occurrence of a symptomatic pathologic fractures, external beam radiation therapy to relieve skeletal symptoms, spinal cord compression, or tumor-related orthopedic surgical intervention, or death from any cause.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to:

- To compare the symptomatic skeletal event-free survival (SSE-FS) of patients on radium-223 vs. placebo while taking randomized ARB therapy.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Assess overall survival (OS)
- Assess time to chemotherapy initiation after RT2 Cycle 1, Day 1 (C1D1)

- Assess radiographic progression-free survival (rPFS) after RT2 C1D1
- Determine the safety profile of androgen receptor blocker (ARB) therapy with or without radium-223
- Assess occurrence of AESI: bone fractures (pathologic and non-pathologic)

2.3 Exploratory Objectives

The exploratory objectives of this study are to:

- Compare the safety and cognitive function of enzalutamide and darolutamide from RT1 randomization through 12 weeks of enzalutamide or darolutamide (prior to RT2)
- Determine skeletal progression using PCWG3 criteria for progression based upon 99Tc bone scan imaging after RT2 randomization
- Determine the time to PSA progression following RT2 randomization
- Determine the total alkaline phosphatase (ALP) response rate every 12 weeks following RT2 randomization
- Assess time to total ALP progression
- Assess time to lactate dehydrogenase (LDH) progression
- Assess further correlative biomarkers in the patient population
- Assess changes in cognitive function following RT2 randomization
- Assess frequency of the following adverse events that are listed as warnings for the study drugs (cardiovascular, seizures, falls, weakness, cognitive function)

2.4 Endpoints

2.4.1 Primary Endpoint

The primary endpoint is the symptomatic skeletal event-free survival (SSE-FS).

Symptomatic skeletal events are defined as the duration of time from RT2 until any one of the following:

- the first use of external-beam radiation therapy to relieve skeletal tumor-related symptoms
- the occurrence of new symptomatic pathologic bone fractures.
- the occurrence of new symptomatic spinal cord compression
- a tumor-related orthopedic surgical intervention

For calculating the cumulative incidence of SSE over time, the time to SSE is defined as the time elapsed between the day of C1D1 after Randomization 2 to the day of SSE recorded for each patient. Patients who are alive and without evidence of an SSE at their last study visit will be censored at that visit date. Patients who die without an SSE will be considered as having a completed event at the date of their death.

2.4.2 Secondary Endpoints

The secondary efficacy endpoints are:

- Overall survival (OS) defined as the time from RT2 randomization until death on study. Patients who are alive at the time of data cut-off will be censored at the last date known to be alive.
- Time to chemotherapy initiation defined as the time from RT2 to initiation of docetaxel or cabazitaxel treatment, whichever occurs earlier.
- Radiological progression-free survival (rPFS) defined as time to the first occurrence of bone scan progression per PCWG3 criteria, and/or progression by CT/MRI per RECIST 1.1 criteria, or death from any cause following RT2. Radiological progression is interpreted by local assessment only.
- Determine the safety profile of androgen receptor blockers (enzalutamide or darolutamide) with or without radium-223 using adverse event rates, electronic patient reported outcomes, and cognitive testing.
- Assess occurrence of AESI: fractures (pathologic and non-pathologic)

2.4.3 Exploratory Endpoints

Exploratory efficacy endpoints include:

- Compare the safety of enzalutamide and darolutamide after 12 weeks of enzalutamide or darolutamide (pre-RT2) using adverse event rates, electronic patient reported outcomes, and cognitive testing.
    - Compare the proportion of subjects meeting criteria for cognitive impairment after 12 weeks of enzalutamide or darolutamide (pre-RT2) by comparing objective neurocognitive tests (CANTAB modules). Cognitive impairment is defined per the International Cognition and Cancer Task Force guidelines as meeting one of the following: 1) ≥1.5 SDs below (age- and education-adjusted) norm on ≥2 cognitive domain modules; or 2) ≥2 SDs below norm on ≥1 cognitive domain module Wefel et al. 2011].
    - Compare the average decline in maximally changed cognitive domain in patients in each treatment group after 12 weeks of enzalutamide or darolutamide (pre-RT2) using objective neurocognitive testing (CANTAB modules).
    - Compare subjective cognitive function between treatment arms by comparing FACT-Cog total scores after 12 weeks of enzalutamide or darolutamide (pre-RT2).
    - Compare overall quality of life between treatment arms by comparing FACT-P between arms after 12 weeks of enzalutamide or darolutamide (pre-RT2)
- Time to first skeletal progression using PCWG3 criteria for progression using 99Tc bone scan imaging after RT2 C1D1.
- Time to PSA progression defined as:
    - For patients with a PSA decline from R2 randomization, an initial PSA increase of at least 25% and 2 ng/mL above the nadir, which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend).

- For patients without a PSA decline from R2 randomization, a PSA increase of at least 25% and 2 ng/mL above the pre-RT2 value.

- Total alkaline phosphatase (ALP) response rate. Total ALP response is defined as the proportion of patients who had elevated total ALP at R2 randomization which has normalized at least 12 weeks after R2 randomization.
- Time to total alkaline phosphatase (ALP) progression defined as:
  - In patients without a total ALP decline from R2 randomization: a ≥25% increase from the value at R2 randomization at least 12 weeks following R2 randomization,
  - In patients with an initial total ALP decline from the value at RT2 randomization: ≥25% increase above the nadir value, which is confirmed by a second value obtained 3 or more weeks later
- Time to lactate dehydrogenase (LDH) progression defined as
  - In patients with normal LDH at RT2 randomization: one abnormally elevated value confirmed by a second abnormal value obtained 3 or more weeks later.
  - In patients with LDH above ULN at RT2 randomization: ≥25% increase from the value at RT2 randomization
- Assess further correlative biomarkers in the patient population
- Assess frequency of the following adverse events that are listed as warnings for the study drugs (cardiovascular, seizures, falls, weakness, cognitive function)

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria in order to be qualified for the first randomization (R1) to Open-label Enzalutamide or Darolutamide (Lead-in Phase):

1. Able and willing to provide informed consent.
2. Progressive mCRPC at screening with histologically or cytologically confirmed diagnosis of prostate adenocarcinoma.
3. Men ≥ 18 years.
4. ECOG performance status of 0 or 1 at screening.
5. Metastatic to bone with ≥ 2 bone metastases (area of increased uptake on ^{99m}Tc bone scan); equivocal lesions on the bone scan must be confirmed by standard X-ray, CT, or MRI.
6. Patients must have progressive castration-resistant prostate cancer (CRPC) on androgen deprivation therapy (ADT) as evidenced by either of:
   a. For patients who manifest disease progression solely as a rising prostate-specific antigen (PSA) level - documentation of a sequence of two rising PSA values at a minimum of 1-week apart with the Screening value ≥1 ng/ml (see Appendix D);
   b. For patients with disease progression manifested in the bone, irrespective of progression by rising PSA – defined by the appearance of 2 or more

new skeletal lesions demonstrated by 99Tc bone imaging. Ambiguous results should be confirmed by other imaging modalities than bone scan and x-ray (e.g.: CT-scan or MRI).

c. For patients with disease progression manifested at nodal sites, irrespective of progression by rising PSA - progression defined per RECIST 1.1.

7. Ongoing ADT with luteinizing hormone-releasing hormone (LHRH) agonist or antagonist or bilateral orchiectomy.
8. Use of bone health agents (denosumab or zoledronic acid or other bisphosphonates) starting any time prior to R1 unless contraindicated or considered not in the best interest of the patient. A waiver must be approved by the medical monitor if bone health agents cannot be used. Bone health agents should be continued throughout both RT1 and RT2 treatment periods.
9. Adequate bone marrow and organ function as defined by:
    a. Hemoglobin ≥ 10.0 g/dL
    b. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
    c. Platelets ≥100 x 10^9/L
    d. Serum creatinine ≤1.95 mg/dL
    e. Estimated creatinine clearance >/= 30 mL/min/1.73m2 by Cockroft-Gault calculation
    f. Alanine aminotransferase (ALT) ≤ 175 U/L
    g. Aspartate aminotransferase (AST) ≤ 100 U/L
    h. Total bilirubin ≤ 1.8 mg/dL (unless the patient a diagnosis of Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin; in patients with Gilbert's, the total bilirubin should be less than 6 mg/dl if patient has Gilbert's and the elevation should be seen in the unconjugated or indirect bilirubin measurement)
    i. LDH ≤ 224 U/L at screening
    j. Albumin ≥2.5 g/dL
10. Fertile male patients, defined as all males physiologically capable of conceiving offspring with female partners of child-bearing potential, must be willing to use condoms plus spermicidal agent during the study treatment period and for 6 months after the last dose of study drug, and not father a child or donate sperm during this period.
11. The treating site investigator deems RT1 (Enzalutamide or Darolutamide) treatment safe and feasible.

Subjects must meet the remaining inclusion criteria in order to be qualified for the second randomization (R2). Only subjects that complete the initial 12 weeks of run-in RT1 should be evaluated. Prior inclusion criteria do not need to be re-evaluated:

12. Patients must have a documented ≥ 30% decline of PSA at any time during the 12 weeks of RT1.

13. Patients must have no evidence of visceral metastatic disease at the time of RT2 randomization.
14. Ongoing treatment with RT1 and bone health agents at time of RT2 randomization.
15. The treating site investigator deems RT2 (Ra-223 dichloride) treatment safe and feasible.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry and will be considered Screen Failures (cannot be randomized to R1). These are only evaluated prior to the first randomization (R1) and do not need to be re-evaluated for R2:

1. Pathological finding consistent with small cell carcinoma of the prostate
2. Prior chemotherapy for CRPC. Prior docetaxel for hormone-sensitive disease is permitted under the following conditions: started within 3 months of ADT initiation, given for a maximum of 6 cycles and progression occurred > 6 months after the last dose of docetaxel.
3. Prior treatment for mCRPC or CRPC. However, the following therapies are permitted and not exclusionary: Sipuleucel-T, 5-alpha-reductase inhibitors, estrogens, or older antiandrogens (such as flutamide, bicalutamide, or nilutamide).
4. Prior treatment for more than 1 month with CYP17 inhibitors (e.g. abiraterone or orteronel)
5. Prior treatment for more than 2 months with agents inhibiting androgen receptor signaling (e.g. enzalutamide, apalutamide, or darolutamide).
6. Prior hemibody or whole-body external radiotherapy. Other types of prior external radiotherapy and brachytherapies are allowed.
7. Prior therapy with radionuclides (e.g., radium-223, strontium-89, samarium-153, rhenium-186, rhenium-188, actinium-225 and lutetium-177).
8. Current involvement in any drug or device trial involving investigational agent or medical device within the last 28 days prior to R1.
9. In general, any prior investigational agent for nmCRPC/mCRPC; however, may be reviewed by medical monitor/PIs for waiver consideration, on a case-by-case basis.
10. Hypersensitivity to compounds related to enzalutamide, darolutamide, or Ra223
11. A blood transfusion ≤ 28 days prior to R1.
12. Major surgical procedures ≤ 28 days or minor surgical procedures ≤7 days prior to R1. No waiting period is required following port-a-cath placement.
13. Patients with visceral metastases, clinical evidence of central nervous system metastases or leptomeningeal tumor spread as demonstrated via CT/MRI of chest, abdomen, pelvis, and CNS (if needed). CT/MRI of the CNS only performed if suspicion of CNS metastases or leptomeningeal tumor spread. Nodules <1 cm alone will not be considered visceral metastases. Renal masses <3cm will not be considered exclusionary.

14. Serious active infection at the time of screening or another serious underlying medical condition that would impair the ability of the patient to receive protocol treatment.
15. Presence of other active cancers, or history of treatment for invasive cancer ≤2 years of study entry. Patients with Stage I/II cancer who have received definitive local treatment and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) and superficial bladder cancer are eligible, as are patients with history of non-melanoma skin cancer.
16. Any other serious or unstable illness, or medical, social, or psychological condition, that could jeopardize the safety of the subject and/or his/her compliance with study procedures, or may interfere with the subject's participation in the study or evaluation of the study results.

3.3 Discontinuation from Randomized Treatments

Following permanent discontinuation of darolutamide, enzalutamide, or Ra-223 or Placebo, patients will have a Telephone End of Study Drug visit, which will include protocol-required safety follow-up assessments 30 days after the last dose of study medication unless the patient specifically declines further follow-up, in which case the data from last visit will be used. Study site personnel must document the patient's decision in the clinical records.

3.4 Required Discontinuation from Randomized (RT1) Treatment (Darolutamide or Enzalutamide)

The primary reasons that require patients to permanently discontinue darolutamide or enzalutamide are as follows:

- Adverse event or inter-current illness: any intolerable adverse event (including toxicity related to ARB) that cannot be ameliorated by the use of adequate medical intervention or that in the opinion of the Site Investigator or Medical Monitor would lead to undue risk if study treatment were continued.
- Gross noncompliance with protocol: the Medical Monitor or Lead-Principal Investigator may request permanent treatment discontinuation in the event of a major protocol deviation, lack of cooperation, or noncompliance.

3.5 Required Discontinuation from Randomized (RT2) Treatment (Ra-233 or Placebo)

The primary reasons that require patients to permanently discontinue the double-blind, randomized Ra-223 or placebo treatment regimen are as follows:

- Radiological disease progression; however, investigators may continue RT2 treatment through 6 cycles until it no longer clinically benefits the patient as defined per PCWG3. PSA progression is not considered progression in this protocol (Scher et al. 2016).
- Adverse event or inter-current illness: any intolerable adverse event (including toxicity related to Ra-223) that cannot be ameliorated by the use of adequate medical intervention

or that in the opinion of the Site Investigator or Medical Monitor would lead to undue risk if study treatment were continued.

- Gross noncompliance with protocol: the Medical Monitor or Lead-Principal Investigator may request permanent treatment discontinuation in the event of a major protocol deviation, lack of cooperation, or noncompliance.
- Required use of a prohibited concomitant therapy (section 8.4.3).
- Death
- Lost to follow-up
- Sponsor discontinuation of study: the Sponsor reserves the right to terminate the study. The Sponsor will terminate this study following completion of the study objectives, or earlier if deemed necessary.
- Patient decision: patients may permanently discontinue any of the randomized study drug treatments at any time for any reason.

3.6 Q12-Week Progression Follow-up

After Ra-223 or placebo (RT2) treatment is completed or discontinued, patients should continue RT1 and have follow-up visits every 12 weeks, until radiological progression, or until a prohibited treatment (section 8.4.3) is initiated. The visits should remain on the same Q12-Week (Imaging) schedule based on Cycle 1, Day 1.

All new reportable AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Site Investigator, these values are not likely to improve. In this case, the Site Investigator must record his or her reasoning for this decision in the patients' medical records and as a comment in the electronic Case Report Form (eCRF).
Once 12-week follow-up visits are no longer required, the patient enters into the Overall Survival phase.

All patients who have Grade 3 or 4 hematological laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v 5.0) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the Site Investigator, not likely that these values are to improve. In this case, the Site Investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment in the eCRF.

3.7 Overall Survival Phase

Patients that have radiological progression or that start a prohibited treatment (section 8.4.3) will be followed every 6 months (+/- 1 month) after the last Q12-Week visit was performed (during randomized (RT2) treatment or during follow-up). Patients will be followed by outpatient visits, telephone contacts, and/or chart review.

Only adverse events identified by the Site Investigator to be related to darolutamide, enzalutamide, radium-223, SSE-related AEs, and Adverse Events of Special Interest will need to be reported.

4. CORRELATIVE TESTING

4.1.1 Planned Use for Biorepository Samples

Subject participation in the central biorepository is optional and will not alter their participation in the overall study.

Sample collection and storage at a central biorepository will enable for future interrogation of prostate cancer biomarkers. At this time the ultimate use of these samples has not been determined; samples may be used to perform various types of analyses, and these analyses will vary depending upon evolving research needs. Potential investigations utilizing stored saliva, serum, plasma, buffy coats, or other tissues include but are not limited to proteins, various metabolites, and others. Samples may also be analyzed for exploratory biomarkers to evaluate predictive biomarkers and to assess correlation with disease activity, effects of study drug, and clinical outcomes.

4.1.2 Biorepository Sample Collection Times

Samples will be collected at 3 timepoints:

- Pre-RT1: Prior to enzalutamide or darolutamide obtained through study.
- Pre-R2: After 12-week Lead-in enzalutamide or darolutamide (RT1), and
- At the next visit after radiographic progression is confirmed or initiation of a prohibited treatment, whichever occurs earlier

4.1.3 Biorepository Sample Collection Information

Details regarding the biorepository sample collection and site responsibilities are available in the laboratory manual.

5. COGNITIVE TESTING AND EPRO

Studies assessing the effect of ADT on the cognitive function of men with prostate cancer have reported mixed results.[McGinty et al. 2014, Alibhai et al. 2010, Joly et al. 2006, Jim et al. 2010] One recent prospective, controlled study of the effect of ADT on cognitive function suggests that treatment with ADT is associated with a decline in cognitive function [Gonzalez et al. 2015]. Additionally, the investigators found a specific SNP that may be associated with increased risk of cognitive dysfunction during treatment but not in untreated men.[Gonzalez et al. 2015] Furthermore, a recent population-based cohort study of men with prostate cancer receiving ADT suggests that ADT may be associated with an increased risk of Alzheimer's disease.[Nead et al. 2016] Whether the cognitive effects associated with treatments with oral therapies that directly

bind the AR in the central nervous system after crossing the blood brain barrier (enzalutamide) when compared with AR targeting agents that do not cross the blood brain barrier (darolutamide), has not been adequately described.

In this study we will assess objective neurocognitive changes associated with treatment with AR targeting agents that do (enzalutamide) and do not (darolutamide) cross the blood brain barrier. Objective neurocognitive change will be compared between arms and longitudinally over time using modules from CANTAB neurocognitive tablet-based tests. A battery of CANTAB cognitive function tests will be used. In addition, we will compare subjective quality of life and neurocognitive effects during treatment with darolutamide and enzalutamide using the ePRO instruments FACT-P and FACT-COG. Data collection will be done electronically at the following timepoints:

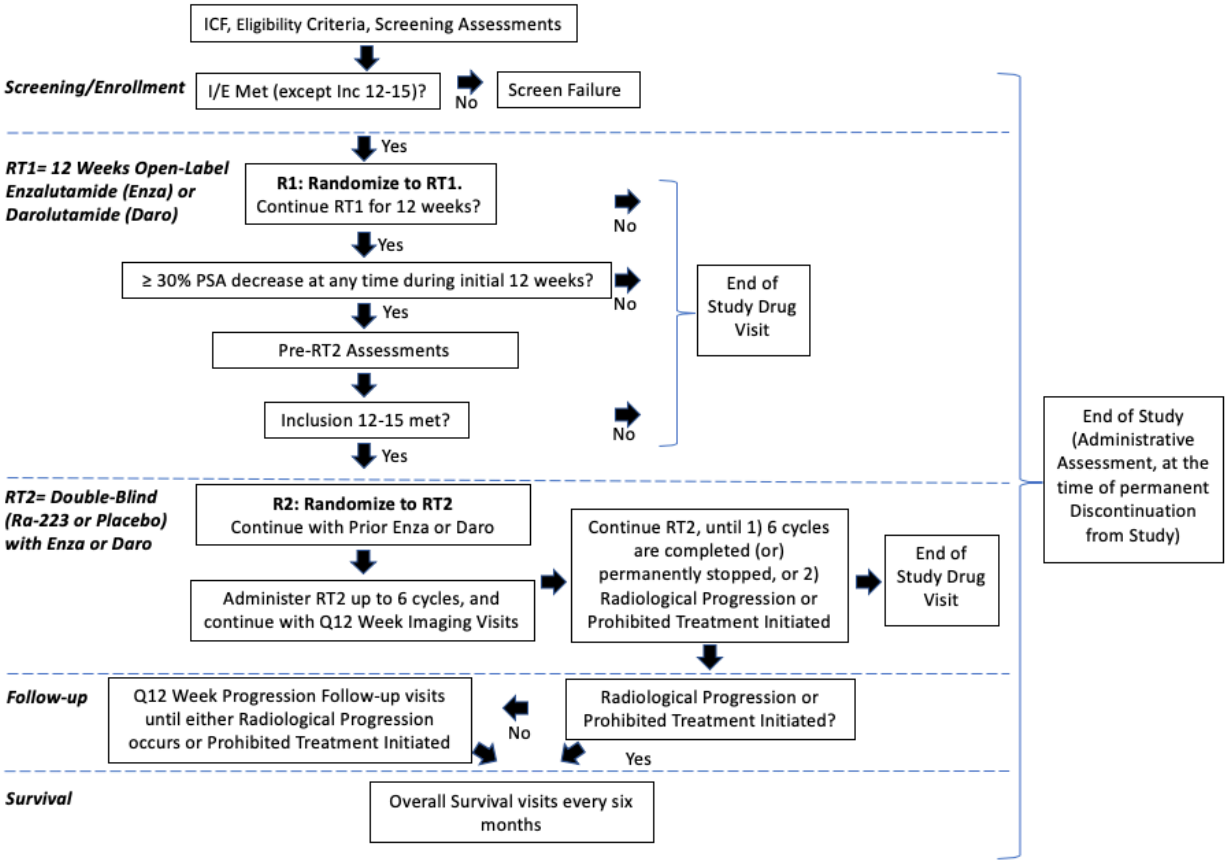
- Screening (practice)
- Pre-RT1 (prior to enzalutamide or darolutamide given through the study)
- Pre-R2 (12 weeks post- enzalutamide or darolutamide)

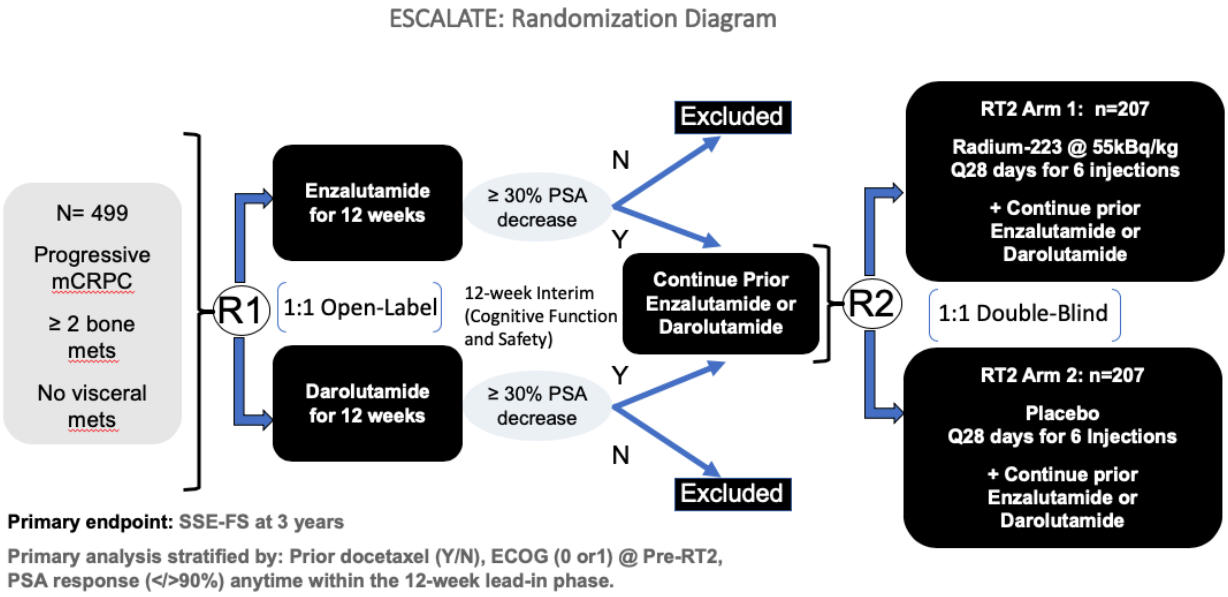
6. STUDY REGISTRATION

The study will be listed on ClinicalTrials.gov by MANA RBM. Yearly updates and reporting on final study results will be the responsibility of MANA RBM.

7. STUDY DESIGN

This is a multi-center, Phase III study in patients with mCRPC.


ICF, Eligibility Criteria, Screening Assessments
Screening/Enrollment
I/E Met (except Inc 12-15)?
No
Screen Failure
Yes
RT1= 12 Weeks Open-Label Enzalutamide (Enza) or Darolutamide (Daro)
R1: Randomize to RT1. Continue RT1 for 12 weeks?
No
Yes
≥ 30% PSA decrease at any time during initial 12 weeks?
No
Yes
Pre-RT2 Assessments
Inclusion 12-15 met?
No
Yes
End of Study Drug Visit
RT2= Double-Blind (Ra-223 or Placebo) with Enza or Daro
R2: Randomize to RT2 Continue with Prior Enza or Daro
Administer RT2 up to 6 cycles, and continue with Q12 Week Imaging Visits
Continue RT2, until 1) 6 cycles are completed (or) permanently stopped, or 2) Radiological Progression or Prohibited Treatment Initiated
End of Study Drug Visit
Follow-up
Q12 Week Progression Follow-up visits until either Radiological Progression occurs or Prohibited Treatment Initiated
No
Radiological Progression or Prohibited Treatment Initiated?
Yes
Survival
Overall Survival visits every six months
End of Study (Administrative Assessment, at the time of permanent Discontinuation from Study)



Screening:

Patients will be screened -42 to -2 days prior to starting RT1 treatment with an androgen receptor blocker.

R1:

Following successful screening for first randomization (i.e., R1 I/E are met), patients will be randomized (R1) 1:1 to open-label randomized treatment 1 (RT1) with either enzalutamide or darolutamide. Patients may not switch RT1 ARB treatment during the study.

RT1: ***Day 1, Day 28, Day 56 and Day 84***

Ensure patient is taking bone health agent (BHA) at or before first RT1 dose and continues on BHA throughout RT1 and RT2 treatment periods. Patients must receive at least 12 weeks of RT1 prior to Pre-R2 visit and before starting randomized, double-blinded Ra-223 or placebo (RT2). Patients will have serial PSAs performed at least every 4 weeks during the first 12 weeks of RT1 therapy.

Pre-R2

Pre-R2 baseline assessments will be done after at least 12-16 weeks of RT1 have been completed and no less than 14 days prior to C1D1 of RT2 to review safety parameters and establish baseline values prior to C1D1. ***Imaging assessments (CT, MRI, Bone Scan) should only be done for patients that have a documented ≥ 30% PSA decline at any time during the first 12 weeks of RT1.***

Subjects must meet additional inclusion criteria 12-15 in order to be qualified for the second randomization (R2). Only subjects that complete the initial 12 weeks of run-in RT1 should be evaluated for the additional inclusion criteria. Prior inclusion criteria 1-11 do not need to be re-evaluated. ***All subjects that complete the lead-in RT1 treatment should perform the second series of Cognitive function testing, even if they do not qualify for R2, prior to discontinuation.***

R2:

If the all (R2) randomization conditions are all met, subjects will be eligible for (R2) randomization and should start the 1st cycle of (RT2) Ra-223 or placebo (C1D1) within 14 days following the pre-R2 safety laboratory blood draw.

Patients eligible for RT2 will be centrally randomized in a 1:1 ratio to receive either radium-223 dichloride or placebo (saline) administered IV on Day 1 of each cycle for 6, 28-day cycles, and will continue with their open-label, randomized ARB and bone health agent(s). The placebo will be administered in precisely the same fashion as the active drug.

RT2, *up to 6 cycles:*

Randomized, Double-Blind Ra-223 or Placebo Cycles 1-6: q 28 days

First RT2 cycle (C1D1) must occur within 14 days after the pre-R2 safety laboratory blood draw. Ideally, subsequent RT2 cycles 2-6 should be scheduled to occur every 28 days +/- 7 days following the previous cycle, but dosing may be delayed up to 4 weeks per cycle (maximum 8 weeks between cycles). Patients will continue with their open-label, randomized ARB irrespective of Ra-223/placebo delays. Subjects should continue on BHA throughout the RT2 treatment period.

Safety laboratory assessments must be completed within 14 days of each cycle and results assessed for safety to proceed with next cycle before administration.

Q12-Week RT2 Imaging

After the first administration of RT2 at C1D1, patients will be assessed radiologically by CT or MRI and bone scan every 12 weeks, until either:

3) radiological progression defined as soft tissue progression per RECIST 1.1 or bone progression per PCWG3 or

4) a prohibited treatment has begun.

The 12-week visits start 12 weeks +/- 7 days after RT2 Cycle 1, Day 1 and must remain on this schedule independent of other study visits. The same imaging modality should be used for all assessments (CT or MRI). The RECIST and PCWG3 tumor assessments should be completed by the same trained rater throughout the study.

Telephone End of Study Drug(s)

Telephone End of Study Drug visits are required 30 days +/- 7 days after last dose of study drug(s) (Ra-223/Placebo, Enzalutamide, and Darolutamide) are administered or at the last clinic visit if patient declines further participation.

Q12-Week Progression Follow-up

After RT2 cycles are either stopped or (6) cycles completed, patients without radiological progression that have not started a prohibited treatment will continue to have clinic visits every 12 weeks (continuing with the same schedule based on C1D1). Enzalutamide or Darolutamide may continue during the Q12-Week Progression Follow-up period. PSA progression alone is not considered progression in this protocol [Scher et al. 2016]. Clinical progression will be assessed by the site investigator on any scheduled or unscheduled visit.

Overall Survival

Patients that demonstrate radiological progression or start a prohibited treatment will be followed for SSE's, AESIs, and overall survival Enzalutamide or Darolutamide may continue during the Overall Survival period. Patients in this phase of the study will be evaluated every 6 months +/- 1 month after the last Q12-Week Visit is performed until death or the end of the study. Patients may be contacted during outpatient visits or by telephone and/or chart review.

End of Study:

When patients permanently discontinue the study due to any reason (screen failure, lost to follow-up, withdrawn consent, etc.), an End of Study visit will be done to capture the reason for screen failure, reason for permanent discontinuation, study disposition, and to assess AEs.

8. STUDY MEDICATIONS

8.1 Randomized Treatment #1, RT1

Ensure patient is taking a bone health agent at time of Randomization 1 (R1). Patients eligible to receive RT1 will be randomized (R1) in a 1:1 ratio to receive open-label enzalutamide (160 mg PO QD) [available commercially through prescription] or darolutamide (600 mg PO BID) [provided through the study] for mCRPC. Dose reductions of RT1 will be allowed per protocol (see dose-reduction guidelines). Once receiving RT1, subjects should continue RT1 on study until toxicity, or other reason listed in section 3.4.

Patients who do not have a ≥ 30% PSA decline at any time during the RT1 period will not be randomized to RT2 and will be discontinued from the study. Patients must receive RT1 at least 12 weeks and meet all R2 conditions to proceed to the second double-blind randomized treatment phase.

8.2 Randomized Treatment #2, RT2

Patients eligible to receive RT2 will be randomized (R2) in a 1:1 ratio to receive double-blind RT2 (radium-223 or placebo) that will be administered IV on Day 1 of each cycle for 6, 28-day cycles). RT2 active and placebo treatments will be administered in precisely the same fashion on Day 1 of each cycle for 6, 28-day cycles. Patients will continue with their open-label, randomized ARB and bone health agent.

Randomized (Ra-223 or Placebo) will be blinded to patient and study staff /investigators who perform any study related procedures/tasks. Designated trained, unblinded individual or individuals will prepare and administer radium-223 at 55 kBq/kg IV or placebo via intravenous infusion on Day 1 of a 28-day cycle for a total of 6 cycles. No dose reductions will be allowed, but treatment can be held for up to 4 weeks. If the hold is the result of a treatment-related AE and lasts for >4 weeks, then treatment will be permanently discontinued. No less than 3 weeks and no more than 8 weeks is allowed between doses. Patients will be evaluated for toxicity within 14 days prior to each cycle. Radiological assessments will be performed every 12 weeks following Cycle 1 Day 1, as defined in Appendix C.

Patients will continue on RT2 for up to 6 cycles or until patient has a reason for discontinuation as listed in Section 3.5 of the protocol.

Upon radiographic progression, further treatments are decided by the site investigator according to standard local practice. Radium-223 or placebo may continue at the discretion of the site investigator (if the maximum of 6 doses have not been reached) if they believe it to be in the patient's best interest. If patient continues on Ra-223 or placebo after radiological progression, the Q12 Week Imaging visits will not be done, and the patient will move into Overall Survival phase after all Ra-223 or Placebo cycles are completed. Enzalutamide or darolutamide may be continued after progression if the treating investigator considers that the patient is still receiving benefit.

PSA progression alone is not considered progression in this protocol [Scher et al. 2016]. Clinical progression will be assessed by the site investigator on any scheduled or unscheduled visit.

8.3 Blinding and Unblinding the Study

8.3.1 Treatment Assignment Unblinding for Blinded Studies

Patients will be randomized to receive radium-223 or placebo in a double-blind fashion. Ideally, there should be at least 2 staff members at each study site who are unblinded in order to allow the individuals to serve as back-up for each other.

All treating physicians, clinical staff, patients, and the sponsor personnel will be blinded as to which treatment a patient is randomized, except for designated and trained unblinded

representatives who will perform drug ordering, drug accountability, preparation of placebo, dose calibration, and administration of Ra-223/Placebo.

There is no intention to routinely unblind individual patients at any time. Individual requests for safety unblinding require the approval of the Medical Monitor. If the investigator decides that unblinding is warranted, the investigator should contact the Medical Monitor prior to unblinding unless this could delay emergency treatment of the participant. The Site Investigator may hold administration of radium-223/placebo while waiting for a decision on unblinding to be made. Approval may be obtained by contacting the Medical Monitor directly. Upon approval by the Medical Monitor, appropriate MANA RBM staff member will break the blind and will provide the site with the patient's treatment assignment.

Examples of circumstances requiring unblinding include:

- A life-threatening, unexpected AE (e.g. SUSAR) that is thought to be related to radium-223 unblinding would change or influence treatment decisions
- In the event of a suspected unexpected serious adverse reaction
- Medication error, such as an accidental overdose, that would warrant unblinding in order to more effectively manage toxicity
- Regulatory reporting requirement (e.g. in the event of a safety signal in a treatment arm.)
- Unblinding influences current treatment decisions (e.g. Ra-223 is a reasonable treatment option for a patient following disease progression)

Site Investigators may only unblind patients under emergency unblinding rules (See unblinding rules document for further details.). If a patient is unblinded by the Site Investigator, he must discontinue Ra-223/Placebo and enter the Overall Survival phase.

The occurrence of a SAE or progressive disease (PD) should not routinely precipitate the immediate unblinding. However, if emergency unblinding is necessary for the treatment of an SAE, study treatment can be unblinded. Should blinding be broken for a patient, the Medical Monitor should be contacted by the Site Investigator within one working day of the premature unblinding to discuss its rationale.

The study will be unblinded for analysis purposes at the time of final analysis.

8.4 Concomitant Medications

At each visit, the patient will be asked about new and ongoing medications taken after the time of the initial informed consent.

8.4.1 Required Concomitant Medications

- **Androgen Deprivation Therapy (ADT)**: all patients who have not had a bilateral orchiectomy are required to remain on a LHRH agonist (e.g. leuprolide, goserelin) or antagonist (e.g. degarelix).

- **Bone Health Agent (BHA)**: all patients are required to take concomitant bone health agents (e.g.,denosumab, zoledronate, or other bisphosphonates) starting prior to the Lead-In RT1 phase and continuing throughout the study unless the site investigator determines there is a contraindication for treatment and requests a medical waiver**. All waivers must be approved by the Medical Monitor.**

8.4.2 Permitted Concomitant Medications and Treatments

All concomitant medications and treatments should be documented in the relevant section of the case report form. Premedication with anti-emetics is allowed according to standard practice guidelines.

Medications may be administered for maintenance of existing conditions prior to screening or for a new condition that develops while on study, including but not limited to the following:

- During the duration of the study, other concomitant treatments including but not limited to treatments such as such as analgesics, corticosteroids, estrogens (e.g., stilboestrol), older antiandrogens (bicalutamide, flutamide, and nilutamide), and ketoconazole are permitted throughout the study according to routine clinical practice at the discretion of the site Investigator.
- Herbal therapies are **not restricted** on study.
- Blood transfusions are allowed throughout the study after R2.
- Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor use, as recommended according to practice guidelines.
- EBRT is allowed at the discretion of the Site Investigator.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the Site Investigator with the exception of those listed in Section 8.4.3.

8.4.3 Prohibited Concomitant Medications

The following treatments are prohibited while in this study:

- Any other investigational therapy
- Radiopharmaceuticals other than study-provided radium-223
- Darolutamide, if RT1 is enzalutamide
- Enzalutamide, if RT1 is darolutamide
- Hemi-body and total body radiation
- Chemotherapy (estramustine (Emcyt™) is considered a chemotherapy)
- Novel CYP17 inhibitors (e.g. abiraterone or orteronel)
- Other novel agents inhibiting androgen receptor signaling (e.g. apalutamide) (Erleada™)
- Immunotherapy
- Bone marrow stimulating agents [sargramostin (Leukine), filgrastim (Neupogen™), pegfilgrastim (Neulasta™) and epoetin alpha (Epogen™, Procrit™)]

8.4.4 Cautionary Medications

- PI should review all concomitant medications that have potential drug-drug interactions with the study medications - Ra-223, enzalutamide, and darolutamide to determine if treatment with the study medications is safe.

9. DOSE MODIFICATIONS

If toxicity occurs, the toxicity will be graded utilizing the NCI CTCAE v 5.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof.

No dose reductions of radium-223 will be allowed. Treatment can be held for up to 4 weeks. If the hold lasts for >4 weeks (>8 weeks between cycles), then treatment will be permanently discontinued. Dose reductions of enzalutamide or darolutamide will be allowed at the discretion of the site investigator during the study, per current full prescribing information.

9.1 Dose and schedule modifications

Dose and schedule modifications are based on recommendations from the investigator's brochure of study medications. At each visit during the treatment period, patients should first be evaluated for the occurrence of adverse events and laboratory abnormalities. Specific recommendations for management of possible adverse events are provided below.

9.1.1 Ra-223

Every effort should be made to administer the full dosing regimen of Ra223 dichloride. Adjustment of dose level is not permitted.

9.1.1.1 Special warnings

• Patients with evidence of compromised bone marrow reserve e.g. following prior cytotoxic chemotherapy and/or radiation treatment (EBRT) should be treated with caution. An increased incidence of hematological adverse reactions such as neutropenia and thrombocytopenia was observed in these patients during the phase III study.
• Crohn's disease and ulcerative colitis: safety and efficacy of Ra-223 in patients with Crohn's disease and with ulcerative colitis have not been studied. Due to the fecal excretion of Ra-223, radiation may lead to aggravation of acute inflammatory bowel disease. Ra-223 should only be administered after a careful benefit-risk assessment in patients with acute inflammatory bowel disease.
• Osteonecrosis of the jaw: in patients treated with bisphosphonates and Ra-223, an increased risk of development of osteonecrosis of the jaw (ONJ) cannot be excluded. In the phase III ALSYMPCA study, cases of ONJ have been reported in 0.67% of patients (4/600) in the Ra223 arm compared to 0.33% patients (1/301) in the placebo arm. However, all patients with ONJ were also exposed to prior or concomitant bisphosphonates (e.g. zoledronic acid) and prior chemotherapy (e.g. docetaxel).

• Secondary malignant neoplasms: Ra-223 contributes to a patient's overall long-term cumulative radiation exposure. Therefore, long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects. In particular, the risk for osteosarcoma, myelodysplastic syndrome and leukemia may be increased. No cases of Ra223-induced cancer have been reported in clinical trials in follow-up of up to three years

9.1.1.2 Dose delay

Dosing delay may be instituted under the following circumstances:

Myelosuppression: treatment-related changes in hematology parameters may occur:
• If a patient experiences CTCAE v4 Grade ≥ 3 neutropenia, thrombocytopenia, or anemia lasting > 14 days, further Ra223 administrations must be discontinued.
• If a patient experiences CTCAE v4 Grade ≥ 3 neutropenia, thrombocytopenia, or anemia the administration of Ra233 should be delayed until recovery to Grade 2 or better.
• Before subsequent administrations, the ANC should be ≥ 1.0 x 109/L and the platelet count ≥ 50 x 109/L.

Gastrointestinal events:
• Diarrhea should be treated as per local practice. A further dose of Ra223 should not be given before diarrhea is recovered to CTCAE v4 Grade 2 or baseline levels.
• Nausea or vomiting should be treated as per local practice. A further dose of Ra223should not be given before nausea or vomiting is recovered to CTCAE v.4 Grade 2 or baseline levels.

Spinal Cord Compression:
In patients with untreated imminent or established spinal cord compression, treatment with standard of care, as clinically indicated, should be completed before starting or resuming treatment with Ra223.

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

Non-pathological fractures:
For traumatic fractures in weight-bearing bones during treatment phase, the Ra223 administration should be delayed for 2-4 weeks from the time of fracture. Orthopedic stabilization of fractures should be performed before starting or resuming treatment with Ra223.

Pathological fractures:
Pathological fractures may occur as the result of either progressive disease or increased physical activity associated with significant pain palliation. Pathologic fractures are to be treated in a

manner that attempts to maintain the best functional status and quality of life. Study treatment may continue as planned.

Any Other Toxicity:
Local practice will apply.

9.1.2 Enzalutamide

If a patient experiences ≥ Grade 3 toxicity or an intolerable adverse reaction, that does not improve with adequate medical intervention, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2.Enzalutamide may be restarted at the original dose (160 mg/day) or at a reduced dose (120 mg or 80 mg) if warranted. After dose reduction, based on patient tolerance, enzalutamide may be reincreased to a maximum dose of 160 mg/day at Investigator discretion.

Enzalutamide must be interrupted during the evaluation of symptoms suspicious of PRES (headache, lethargy, confusion, blindness and other visual and neurological disturbances, with or without associated hypertension). Restarting treatment at a reduced dose or after treatment interruption for > 2 weeks must be discussed with the Medical Monitor.

9.1.3 Darolutamide

NUBEQA (Darolutamide): If a patient experiences a greater than or equal to Grade 3 toxicity or an intolerable adverse reaction, withhold dosing or reduce to 300 mg twice daily until symptoms improve. Then the treatment may be resumed at a dose of 600 mg twice daily. Dose reduction below 300 mg twice daily is not recommended

10. STUDY ASSESSMENTS AND EVALUATIONS

10.1 Overview

All patients should visit the study center on the days and windows specified within this protocol. The complete Schedule of Assessments for this study is shown in Appendix C, page 94. Visits may be split over multiple days if needed and may be conducted via remote visits (non-clinic) or via telemedicine visits as needed to facilitate visit completion and infection control (e.g. limit COVID-19 exposure).

10.2 Screening

- Written informed consent prior to any study-related procedures

Screening assessments that can be done up to ≤42 days prior to Lead-in RT1:

- Bone scan

- CT scan of the chest, abdomen and pelvis (preferred modality) given with IV contrast unless contraindicated. An MRI may be used in place of a CT scan. The same modality must be used throughout the study.
- MRI or CT scan of the brain, if indicated by clinical symptoms, ≤4 weeks prior to randomization
- Begin prescription/insurance process for obtaining commercial Enzalutamide (for all subjects, in case RT1 is Enzalutamide)

Screening assessments that can be done up to ≤28 days prior to Lead-in RT1:

- Physical examination
- Demographics
- ECOG performance status (see Appendix A), page 77.
- Vital signs measurements of height (first visit only), weight, resting heart rate, blood pressure, respiratory rate, and temperature)
- Concomitant medication review - all ongoing medications.
- Prior anticancer/relevant medication and procedure history review- including history of androgen deprivation therapy, orchiectomy, radical prostatectomy, history of prior bisphosphonate/ denosumab use, vitamin D, calcium, anticancer medications, and exclusionary medications.
- Cognitive Assessments Practice (Battery of CANTAB Cognitive Function Tests)
- ePRO Assessments (FACT-P, FACT-COG)
- 12-lead ECG
- Screening bone fracture risk assessment: This includes a history of prior fractures, comorbidities, prior bone density assessment (particularly the most recent bone density assessment prior to screening).
- Past and ongoing medical history

Screening assessments that can be done up to ≤14 days prior to Lead-in RT1:

- CBC: including hemoglobin, hematocrit, white blood cell (WBC) with 3-part differential, and platelets
- CMP: including glucose, blood urea nitrogen (BUN), creatinine, estimated creatinine clearance (Cockcroft-Gault), sodium, potassium, chloride, calcium, carbon dioxide (CO_2), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total protein, and albumin.
- ALP and LDH
- PSA
- Research biomarkers, with optional patient consent
- If not already taking, start treatment with bone health agent if not contraindicated.
- Eligibility review

If all I/E are met (except inclusion criteria 12-15), subject may proceed to Randomization (R1). PCWG3 read of Screening Bone scan will be performed for all subjects that get randomized to R2, so that 2+2 rule can be evaluated.

10.3 Lead-In RT1 (enzalutamide or darolutamide) Therapy Phase (12 weeks duration)

- Lead-In RT1/: Day 1 only, prior to first dose of RT1
  - ePRO Assessments (FACT-P, FACT-COG)
  - ECOG performance status
  - TUG (timed up and go)
  - Cognitive Assessments (Battery of CANTAB Cognitive Function Tests)
- Enzalutamide or Darolutamide Estimated Compliance (RT1 Days 28, 56, and 84 only)

- All RT1 visits (Day 1, Day 28, Day 56, and Day 84)
  - Darolutamide Dispensation (if applicable)
  - Darolutamide Accountability (if applicable)
  - PSA blood sample will be collected at least every 4 weeks (+/- 7 days)
  - Adverse event evaluation
  - Assessment of bone fractures (AESIs) and SSEs

10.4 Pre-R2 Assessments, at 12-16 weeks after RT1 initiation, within 14 days prior to RT2 randomization.

- Abbreviated Physical Exam
- Vital signs: weight, resting heart rate, blood pressure, respiratory rate, and temperature.
- ECOG performance status
- ePRO Assessments (FACT-P, FACT-COG)
- Cognitive Assessments (Battery of CANTAB Cognitive Function Tests)
- TUG (timed up and go)
- 12-lead ECG
- Adverse event (AE) assessment
- Concomitant medication review
- CBC including hemoglobin, hematocrit, WBC with 3-part differential and platelets
- CMP including glucose, BUN, creatinine, estimated creatinine clearance (Cockcroft-Gault), sodium, potassium, chloride, calcium, CO_2, AST, ALT, total bilirubin, total protein, and albumin.
- ALP and LDH
- PSA
- Research biomarkers, with optional patient consent
- Assessment of bone fractures (AESIs) and SSEs
- Review of other anti-cancer therapies
- Bone fracture assessment
- SSE evaluation

- Enzalutamide or Darolutamide Estimated Compliance
- Darolutamide Dispensation (if applicable)
- Darolutamide Accountability (if applicable)

NOTE:

- A CT or MRI and Bone scan should only be done for subjects that meet inclusion criterion 12. After imaging results are available, subjects should continue to be reviewed for inclusion 13-15.
- RECIST/PCWG3 assessments associated with the Pre-R2 CT or MRI and Bone scans must be done for patients that meet (all) Inc/Exc. (including inclusion criteria 12-15) and randomize to R2.

If the Inclusion Criteria 12-15 are met, the patient may proceed to second randomization (R2).

10.5 Ra-223 or Placebo Administration Cycles 1-6 (every 4 weeks)

Day 1 of each cycle (up to 14 days prior to Ra-223 or Placebo administration)

- Vital signs: weight, resting heart rate, blood pressure, respiratory rate, and temperature.
- ECOG performance status
- Adverse event (AE) assessment
- Abbreviated Physical Exam (C4D1 only)
- Concomitant medication review
- Review of other anti-cancer therapies
- Assessment of bone fractures (AESIs) and SSEs
- Review of other anti-cancer therapies
- CBC including hemoglobin, hematocrit, WBC with 3-part differential and platelets
- CMP including glucose, BUN, creatinine, estimated creatinine clearance (Cockcroft-Gault), sodium, potassium, chloride, calcium, CO_2, AST, ALT, total bilirubin, total protein, and albumin.
- ALP and LDH
- PSA
- Research biomarkers, with optional patient consent, at the next visit following confirmed radiographic progression or prior to initiation of a prohibited treatment only, whichever occurs earlier
- Administration of Ra-223 or placebo (only after the site investigator deems it is safe for patient to be dosed after review of the above)
- Enzalutamide or Darolutamide Estimated Compliance
- Darolutamide Dispensation (if applicable)
- Darolutamide Accountability (if applicable)

10.6 12-Week Imaging Visits

Patients will be evaluated for response to treatment every 12 weeks (+/- 7 days). Visits should be scheduled from the first dose of radium-223 or placebo (Cycle 1, Day 1) regardless of treatment delays. The following assessments will be performed:

- CT scan of the chest, abdomen and pelvis (preferred modality), given with IV contrast unless contraindicated. An MRI may be used in place of a CT scan. The same modality must be used throughout the study.
- Bone scan
- RECIST
- PCWG3 assessment (bone scan)
- Assessment of bone fractures (AESIs) and SSEs
- Adverse event assessment

All radiographic scans (CT, MRI and bone scans) will be collected and held in the site's eISF.

10.7 Telephone End of Study Drug Visit

The following evaluations are required 30 days +/- 7 days after the last dose of RT1 (enzalutamide or darolutamide) and/or RT2 (radium-223/placebo). Separate visits may be required, in the event RT1 and RT2 are not discontinued simultaneously. If repeat labs are needed, unscheduled labs may be done.

- Adverse event (AE) assessment - all AEs must be followed for 30 calendar days after the last dose of study medication(s)
- Concomitant medication review
- Assessment of bone fractures (AESIs) and SSEs
- Review of other anti-cancer therapies

10.8 Q12 Week Progression Follow-up Visits

After completion or discontinuation of randomized Ra-223 or placebo treatment (RT2), patients without radiological progression that have not started a prohibited treatment will have visits every 12 weeks (±7 days) to monitor for radiological progression post completion or discontinuation of Ra-223.

During this phase, all assessments should occur according to the original radiology schedule (every 12 weeks following C1D1). The following assessments will be performed until either radiologic progression or start of a prohibited treatment:

- Vital signs: weight, resting heart rate, blood pressure, respiratory rate, and temperature.
- Adverse event (AE) assessment - only adverse events identified by the site investigator to be related to radium-223 (i.e. new primary malignancies, chronic myelosuppression, etc.), darolutamide, or enzalutamide AEs, SSE-related AEs, and adverse events of special interest
- Review of other anti-cancer therapies
- Concomitant medication review

- CBC including hemoglobin, hematocrit, WBC with 3-part differential and platelets
- CMP including glucose, BUN, creatinine, estimated creatinine clearance (Cockcroft-Gault), sodium, potassium, chloride, calcium, CO_2, AST, ALT, total bilirubin, total protein, and albumin
- PSA
- ALP and LDH
- Research biomarkers, with optional patient consent, at the next visit following confirmed radiographic progression or prior to initiation of a prohibited treatment, whichever occurs earlier
- CT scan of the chest, abdomen and pelvis (preferred modality), given with IV contrast unless contraindicated. An MRI may be used in place of a CT scan. The same modality must be used throughout the study.
- Bone scan
- RECIST and PCWG3 assessment
- Assessment of bone fractures (AESIs) and SSEs
- Survival status
- Enzalutamide or Darolutamide Estimated Compliance
- Darolutamide Dispensation (if applicable)
- Darolutamide Accountability (if applicable)
- The following are required every 48 weeks after C1D1:
    - ECOG performance status
    - ePRO Assessments (FACT-P, FACT-COG)
    - TUG (timed up and go)
    - 12-lead ECG

10.9 Overall Survival

Patients that have radiological progression or start a prohibited treatment will be followed every 6 months (+/- 1 month) after the last Q12-Week Imaging Visit showing progression is performed (during RT2 treatment or during follow-up).

Patients will have visits until the required number of events for the primary endpoint has been reached or death, whichever comes first. Patients may be contacted during outpatient visits or by telephone and/or chart review. Subjects continuing on darolutamide may be re-supplied with study medications between visits.

The following assessments will be performed:

- Assessment of bone fractures (AESIs) and SSEs
- Review of other anti-cancer therapies
- AE assessment - Only adverse events identified by the site investigator to be related to radium-223, enzalutamide, or darolutamide (i.e. new primary malignancies other than basal cell carcinoma, chronic myelosuppression, etc.), SSE-related AEs, and adverse events of special interest
- Enzalutamide or Darolutamide Estimated Compliance

- Darolutamide Dispensation (if applicable)
- Darolutamide Accountability (if applicable)
- Survival status

10.10 End of Study Administrative Assessments

When patients permanently discontinue the study due to any reason (screen failure, lost to follow-up, withdrawn consent, etc.), End of Study Administrative Assessments will capture the reason for permanent discontinuation and will record:

- Reason for Discontinuation
- Study Disposition
- For subjects that are still in contact with the site and have not withdrawn consent: AE assessment via outpatient visit or by telephone and/or chart review.
    - Adverse events identified by the site investigator to be related to radium-223 (i.e. new primary malignancies other than basal cell carcinoma, chronic myelosuppression, etc.) or darolutamide, SSE-related AEs, and adverse events of special interest.
- Public Records Search: any Deaths that occur after Early Termination (if known).

10.11 Lost to Follow-up

Attempts to locate patients should be documented via phone contacts and certified letter. At least three (3) documented phone calls and (1) certified letter should be attempted in an effort to reinstate contact. If no response from contact attempts, the patient can be considered lost to follow-up. Patients that are lost to follow-up should still be followed for survival status using available methods for public records search. The method for search used to confirm death, date of death and cause of death (if known) will be entered into the EDC- End of Study Record and the public record should be filed to the patient's eISF PHI folder.

11. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

11.1 Radium-223

Investigational Product	Dosage Form and Strength	Manufacturer
Radium-223	1,100 kBq/mL	Algeta's Institute for Energy Technology

The alpha-pharmaceutical radium-223 is a ready-to-use, sterile, non-pyrogenic, clear and colorless aqueous solution of radium-223 dichloride ($^{223}RaCl_2$) for IV administration. It should not be diluted or mixed with any solutions. Each vial is for a single use only.

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

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

11.1.1 Labelling, Packaging, and Supply

Radium-223, is manufactured for Bayer Consumer Care AG by the contract manufacturer Algeta 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 or pre-filled syringe, ready-to-use with a certified activity. Radium-223 is shipped in a lead container and Type A radioactive package according to international transportation guidelines for radioactive materials.

For study sites in the US, it is possible to have patient-ready doses (PRD) prepared by the country depot. Dose will be delivered to the sites in pre-filled syringes. Both radium-223 and placebo syringes will be covered with a label masking the syringe content.

The investigational drug is supplied in single-use vials containing 6 mL of solution at a concentration of 1,100 kBq/mL (30 microcurie/mL) with a total radioactivity of 6,600 kBq/vial (178 microcurie/vial) at the reference date. Radium-223 has a shelf life of 28 days from production day, when stored at ambient temperature. The shelf life has been demonstrated for temperatures from cold storage (2-8°C) up to 40°C. In addition, it has been shown that the product quality is not jeopardized upon freezing. The shelf life should not be confused with the half-life of Radium-223 which is 11.4 days.

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

11.1.2 General warning

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

11.1.3 Radiation protection

The administration of radium-223 is associated with potential risks for other persons (e.g., medical staff, caregivers, 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. Since the study is blinded, radiation protection must be in place for patients, blinded staff, and members of the patient's family, even when placebo is administered.
The immediate packaging will contain a statement to conform with U.S. Food and Drug Administration (FDA) Investigational New Drug (IND) requirements as follows:
"Caution: New Drug – Limited by Federal (or United States) law to investigational use."

All study drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for radium-223 are included on the investigational product label.

11.1.4 Preparation and Administration of Radium-223

11.1.4.1 Dose preparation

Personnel should use appropriate protective clothing and equipment during syringe filling (if applicable) and application to prevent contamination with the radioactive solution (medical gloves / protective glasses). For sites receiving radium-223 in a vial, the individual responsible for study drug preparation will draw the correct volume of study drug from the vial into a syringe. The size of the syringe should be chosen according to the applied volume to reach the required dosing accuracy.
Radium-223 should not be diluted or mixed with any solutions. Do not store above 40°C (104°F). If the vials or pre-filled syringes 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-223 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.

11.1.4.2 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-223. The syringe should be handed over to the individual who will perform the injection. The study medication will be administered as a bolus IV injection over approximately 1 minute.

After administration, the equipment used in connection with the preparation and administration of drug (including placebo) is to be treated as radioactive waste and should be disposed in accordance with local procedure for the handling of radioactive material.

The dosage regimen of radium-223 injection is 55 kBq (1.49 microcurie) per kg body weight, given at 4-week intervals. Safety and efficacy beyond 6 injections with radium-223 have not been studied.

The volume to be administered to a given patient should be calculated using the:

- Patient's body weight (kg)
- Dosage level 55 kBq/kg body weight or 1.49 microcurie/kg body weight
- Radioactivity concentration of the product (1,100 kBq/mL; 30 microcurie/mL) at the reference date.
- Decay correction factor to correct for physical decay of ^{223}Ra.

The total volume to be administered to a patient is calculated by the formula below:
Volume to be administered (mL) = (Body weight in kg x 55 kBq/kg body weight)/ (Decay factor x 1,100 kBq/mL)

The Decay Correction Factor is determined from the Table below:

Decay Correction Factor Table

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

The Decay Correction Factor Table is corrected to 12 noon Central Standard Time (CST). To determine the decay correction factor, count the number of days before or after the reference date. The Decay Correction Factor Table includes a correction to account for the 7-hour time difference between 12 noon Central European Time (CET) at the site of manufacture (Norway) as 12 noon US CST, which is 7 hours later than CET.

Immediately before and after administration, the net patient dose of administered radium-223 should be determined by measurement in an appropriate radioisotope dose calibrator that has been CT and corrected for decay using the date and time of calibration. The dose calibrator must be calibrated with nationally recognized standards, carried out at the time of commissioning, after any maintenance procedure that could affect the dosimetry and at intervals not to exceed one year. The dose calibration procedure should be conducted by an unblinded person in a location where blinded persons are prohibited entry. Dose calibration data must be recorded in a manner that cannot be viewed by the site investigator or any other study personnel. Clinical monitors must confirm the security of the unblinded procedures and data.

Additional details will be included in the Ra-223/Placebo section of the Study Medication Guide.

11.1.5 Precautions and Risks Associated with radium-223

Please refer to the Xofigo Full Prescribing Information for information regarding precautions and risks.

11.2 Enzalutamide

Enzalutamide is to be administered in accordance with the terms of its marketing authorization and in accordance with institutional standard of practice. Subjects randomized to enzalutamide at R1 will be expected to take 160 mg PO QD after R1 during the lead-in RT1 period and the

RT2 period. After RT2 period is concluded, it may be continued until no longer providing benefit or per site's standard of care. Dose reductions are allowed to manage adverse events or toxicities.

Subjects will be asked about their compliance taking the prescribed enzalutamide at routine visits and will be asked to bring their prescription bottles to clinic visits for verification that prescriptions are being filled.

11.2.1 Labelling, Packaging, and Supply

Patients randomized to open-label enzalutamide at R1 will be given a prescription to obtain commercial enzalutamide.

11.3 Darolutamide

Darolutamide is to be administered in accordance with the terms of its marketing authorization with the exception of indication. Darolutamide is not currently indicated for patients with mCRPC. In this study, subjects randomized to darolutamide at R1 will receive 600 mg PO BID through the study and will be expected to take darolutamide after R1 during the lead-in RT1 period and the RT2 period. After RT2 period is concluded, it may be continued until no longer providing benefit. Dose reductions are allowed to manage any adverse events or toxicities.

Subjects will be asked about their compliance taking darolutamide at routine visits and will be asked to bring partial and empty dispensed bottles to clinic visits to measure compliance.

11.3.1 Labelling, Packaging, and Supply

Patients randomized to open-label darolutamide at R1 will be provided with darolutamide sourced through the study.

Additional details will be included in the darolutamide section of the Study Medication Guide.

11.4 Accountability for All Study Drugs

The Site Investigator (or designee) is responsible for accountability of all used and unused study drugs (Ra-223 or Placebo, and darolutamide only) supplies at the site.

Double-Blinded Drug Accountability
All study drug inventories for Ra-223 or Placebo must be made available for inspection by the (unblinded) Sponsor or its representatives and regulatory agency inspectors upon request. Drug accountability data will be collected on electronic forms viewable only by unblinded study staff. Any paper records (e.g., shipment forms) will be certified as electronic copies and uploaded to a separate unblinded area of the eISF. Accountability data for Ra-223 or Placebo will only be assessible by designated/trained unblinded monitor(s) and unblinded study staff. Documentation of IP chain of custody will also be included in the Site's electronic Investigator Site File archive.

As the Sponsor, MANA RBM's unblinded staff will access electronic records to perform checks of drug storage, dispensing procedures, and accountability records for Ra-223 or Placebo.

Open-Label Drug Accountability
All study drug inventories for darolutamide must be made available for inspection by the Sponsor or its representatives and regulatory agency inspectors upon request. Drug accountability data will be collected on electronic forms. Any paper records (e.g., shipment forms) will be certified as electronic copies and uploaded to the eISF. Documentation of IP chain of custody will also be included in the Site's electronic Investigator Site File archive. As the Sponsor, MANA RBM central reviewers will access electronic records to perform checks of drug storage, dispensing procedures, and accountability records. Darolutamide accountability activity oversight will be performed by the central reviewers and monitor remotely using electronic records completed by the study site.

12. RESPONSE EVALUATIONS AND MEASUREMENTS

Skeletal response will be evaluated using PCWG3 measured by 99Tc bone scan imaging. Soft tissue response will be evaluated in this study using RECIST 1.1 (see Appendix D). Soft tissue lesions are either measurable or non-measurable according to the criteria. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Radiological progression will be interpreted by local assessment only.

13. STATISTICAL CONSIDERATIONS

13.1 Statistical Design

This is a randomized, multi-center, double-blind, Phase III study of radium-223 plus enzalutamide or darolutamide compared to enzalutamide or darolutamide treatment plus placebo.

13.2 Stratification factors

The following stratification variables will be used in the RT2 randomization process:

- PSA response (≥90% vs < 90% decline at any time from initiation of RT1)
- ECOG Score 1 or 0 at Pre RT2 visit
- Prior docetaxel use (yes vs no)

13.3 Sample Size Considerations

1:1 randomized Phase III study with primary endpoint of SSE-FS
Assumptions: based on information provided by Bayer.

- The ERA-223 study (published data) suggests that the median SSE-FS rate for the placebo control are is 24 months, as per the Bayer adjustment of -4 months.
- HR = 0.70
- Median SSE-FS for enzalutamide of 34.3 months (under the exponential assumption).
- Two-sided alpha = 0.05
- Power = 0.80
- Cumulative drop-out rate by the end of the study = 10%

Therefore:

Power	Recruitment Period (months)	Follow-up Period (months)	Expected Number of Events	Total Number of Patients Randomized at R2
80%	18	32	246	414

No interim analysis for efficacy or futility is being planned.

Fifty nine percent of patients randomized would be expected to contribute with an event. Under the expectation that 83% **[per Bayer]** of RT1 patients would have a ≥ 30% decrease in PSA within 12 weeks, then a total of 499 patients would be involved in the first randomization (RT1), to yield the 414 patients needed for the second randomization (RT2).

13.4 Analysis Population

The following analysis populations will be used:

- Full Analysis Set is defined as all patients randomized. Patients will be included in the treatment group to which they were randomized, following the intent-to-treat principle.
- Safety Analysis Set is defined as all randomized patients who have received at least one dose of at least one of the study treatments (enzalutamide, darolutamide, radium-223 or placebo). Patients will be included in the treatment group in which they have been actually treated.

13.5 Data Analysis

Descriptive statistics, including mean, median, standard deviations and ranges for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time-to-events endpoints will be reported using Kaplan-Meier estimates, with 95% CI for median time-to-event.

13.5.1 Demographics and Baseline Characteristics

Demographic and disease characteristics prior to lead in treatment as well as prior to randomization will be summarized in order to assess the comparability of the treatment groups

descriptively. Data to be tabulated will include demographic features such as age, ethnicity, race, and highest level of education as well as disease-specific characteristics.

The number and percentages of patients screened, treated in the lead-in portion, randomized, who received randomized study drug treatment, and who were withdrawn from treatment/study for any reasons will be presented overall and also by treatment group.

13.5.2 **Efficacy Analysis**

All efficacy analyses will be performed using the Full Analysis Set.

The SSE-FS, rPFS, time to total ALP progression, time to first skeletal progression, time to LDH progression, time to chemotherapy, and overall survival will be compared between the two arms using a stratified log-rank test with the same stratification factors as for randomization. The HR (radium-223 dichloride / placebo) will be computed together with the 2-sided 95% CI using a Cox regression model stratified by the same factors. Kaplan-Meier estimates and plots for both treatment groups will be produced to accompany these analyses.

The median, 2- and 3-year event free rates with associated 95% CI will be generated. Additional details, including detailed censoring rules for these endpoints will be described in a separate statistical analysis plan (SAP). For ALP and LDH response rate, the estimates and associated 95% CI (Clopper et al. 1934), in each treatment group will be calculated. The absolute and relative difference in rate estimates between the two treatment groups will also be presented.

13.5.3 **Safety Analysis**

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy after randomization 1 and will be graded according to NCI CTCAE 5.0. A copy of CTCAE scoring system may be downloaded from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

The AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized using system organ class and preferred term by treatment group for all patients in the Safety Analysis Set. In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented by treatment group.

Other safety endpoints, including laboratory results and vital signs findings, will be summarized for all patients in the Safety Analysis Set.

Concomitant medications will be coded using the World Health Organization Drug Dictionary and they will be listed and summarized by treatment group for the Safety Analysis Set.

13.6 Analysis Time Points

13.6.1 Planned Interim Analyses

Interim analyses to compare the safety and cognitive function of enzalutamide and darolutamide after RT1 randomization through 12 weeks of enzalutamide or darolutamide (prior to RT2) is planned. The details and timing of the planned interim analyses will be fully described in the Statistical Analysis Plan.

After 25% of patients complete Randomization 2 and are followed for 9 months, a safety analysis focusing on fractures and death between the blinded arms, with and without radium-223 will be carried out by the IDMC.

13.6.2 Final Analysis

The final analysis of the study will occur after the last visit of the last patient.

13.7 Primary Completion Date

The primary completion date is defined as the date on which the last participant in the study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ends according to the protocol or is terminated early does not affect this date.

13.8 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will be formed for this study.
The specific roles and responsibilities of the IDMC and its members will be documented and described in a separate document.

Special analyses of rates of falls, seizures, cardiovascular events (MI's, sudden death, angina, hypertension, heart failure), fatigue, and neurocognitive decline will be evaluated as part of the IDMC safety evaluation.

13.9 Steering Committee

The Steering Committee will be chaired by Dr. Neal Shore, Study Lead-Principal Investigator.
The specific roles and responsibilities of the Steering Committee and its members will be documented and described in a separate document.

14. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording AEs, AESIs and SAEs, measurement of protocol-specified hematology and clinical chemistry variables, measurement of protocol-specified vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Site Investigator is responsible for recognizing and reporting AEs using the electronic data collection system. It is the Sponsor's responsibility to report SUSARs to the applicable local, national, or international regulatory bodies. In addition, Site Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of that IRB.
The Site Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

14.1 Definitions

14.1.1 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An adverse event (also known as adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose including overdose.

14.1.2 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are events of scientific and clinical interest specific to the safety profile of the study treatment regimen and may require close safety monitoring, reporting of events within 24 hours of the first knowledge of the event by the treating physician or research personnel, and will be considered in all safety analyses. An AESI may be either a serious or non-serious event.

Adverse events of special interest for the combination of radium-223 plus enzalutamide or darolutamide in mCRPC patients include bone fractures. Appropriate efforts should be made to rule out disease progression or other etiologic cause of the AESI. If the Site Investigator has any questions regarding an AE being an AESI, they should immediately contact the Medical Monitor. These will be collected for the duration of the study, even after the patient has discontinued therapy.

Adverse events of special interest observed in this study include:

- All bone fractures, either pathologic or non-pathologic.

14.1.3 Serious Adverse Event

An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization of at least 24 hours or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

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

It is important to distinguish between "serious" and "severe" AEs, as the terms are not synonymous. "Severity" is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. Seriousness serves as the guide for defining regulatory reporting obligations. "Serious" is a regulatory definition and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea which persists for several hours may be considered severe nausea but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

All SAEs will be reported to the FDA upon completion of the study in the final study report.

14.1.4 Suspected Unexpected Serious Adverse Reactions (SUSAR)

MANA RBM will be responsible for determining whether the SAE meets the criteria for a SUSAR and will report any relevant potential SUSARs to Bayer Consumer Care AG (Ra-223 or darolutamide) or the FDA (enzalutamide).

14.2 Recording and Reporting of Adverse Events

14.2.1 Recording of Adverse Events

All AEs and SAEs of any patient during the course of the research study will be recorded in the EDC, and the Site Investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration and the drug that is suspected, if related).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes an SAE or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the Site Investigator's assessment of causality (i.e., the relationship to the study treatment[s]). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE v5.0, and changes will be documented.

Serious Adverse Events will be reported by the research sites using the EDC system within 24 hours of the site being notified of the SAE. MANA RBM will evaluate each SAE to determine whether it meets the criteria for a SUSAR. All SAEs will be reported in the Clinical Study Report at the end of the study. SUSARs will be immediately reported to the FDA (and Bayer Consumer Care AG for those related to Ra-223 or darolutamide). Death related to disease progression is not considered a SAE and will be reported as part of the overall survival assessment.

Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms, abnormal test findings, changes in physical examination; hypersensitivity; and other measurements that occur will be reported as an AE and collected on the relevant eCRF screen.

Test findings will be reported as an AE if: the test result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or test findings require additional testing or surgical intervention, a test result or finding is associated with accompanying symptoms, or a test result that is clinically significant by the Site Investigator is considered to be an AE.

14.2.2 **Reporting Period for Adverse Events**

All AEs will be reported regardless of seriousness or relationship to radium-223 or placebo treatment or enzalutamide/darolutamide, spanning from the period from signing the informed consent until 30 calendar days after discontinuation of these treatments (whichever is discontinued last).

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the Site Investigator, the AE or laboratory abnormality is/ are not likely to improve because of an underlying disease. In this case, the Site Investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF screen.

After 30 days following completion of protocol-specific treatment or discontinuation (end of study drug visit), AEs, SAEs, or deaths assessed by the Site Investigator as treatment-related are to be reported. In addition, AESIs and SSE-related AEs (e.g. bone pain requiring EBRT) are to be reported.

SSEs and AESIs are reported throughout the study. These are the only adverse events to be reported after the final end of study drug visit.

14.2.3 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning; or detected through physical examination, laboratory test, or other means, will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, Site Investigators should apply the following general guideline:

YES: There is a plausible temporal relationship between the onset of the AE and administration of the study medication, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug; and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.

NO: Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

14.3 Recording and Reporting of Adverse Events of Special Interest

All AESIs and SSEs regardless of seriousness or relationship to the study medications, spanning from the start of randomized study treatments until the subject completes the study are to be reported using the EDC system within 24 hours of the first knowledge of the event by the treating physician or research personnel. Additional data will be collected for all AESI.

14.4 Recording of Adverse Events and Serious Adverse Events

14.4.1 Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Site Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at

the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) in the EDC. If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method, should not be reported as an SAE.

14.4.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate AE or SAE with the relevant change in severity captured in the EDC.
A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. Each instance of the AE should be recorded with appropriate start and stop dates in the EDC.

14.4.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF screen. All ≥CTCAE Grade 2 will be flagged for review of clinical significance by site investigator.

Abnormal laboratory values will be reported as an AE if laboratory result or finding is associated with accompanying symptoms, laboratory result is ≥CTCAE Grade 3, or is considered to be clinically significant by the Site Investigator.

Abnormal laboratory values will also be reported as an AE if laboratory result requires:

- adjustment in the study drug(s)
- discontinuation of treatment
- additional testing, or
- surgical intervention

14.4.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Site Investigator solely to progression of disease will be recorded on the "End of Study" eCRF screen. All other on-study deaths, regardless of attribution, that occur within the protocol-

specified AE reporting period will be recorded on an SAE Report Form within the EDC within 24 hours of being notified of the death.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE/SAE Report Form in the EDC. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF Adverse Event screen.

14.4.5 **Hospitalization, Prolonged Hospitalization, or Surgery**

Any AE that results in hospitalization of >24 hours or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.
Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency department or emergency room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, custodial care or respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as an SAE.

14.4.6 **Pre-Existing Medical Conditions**

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical History eCRF page. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE/ SAE EDC Case Report Form, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

14.4.7 **New Cancers**

The development of a new primary cancer, other than non-melanoma skin cancer, should be regarded as an SAE and will generally meet at least one of the seriousness criteria. These will be collected for the duration of the study, even after treatment discontinuation. New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer.

14.4.8 **Radium-223 Overdose**

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Medical Monitor no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting if the overdose is symptomatic.

For information on how to manage an overdose of radium-223, see the Ra-223 Full Prescribing Information.

14.5 Sponsor Serious Adverse Event Reporting Requirements

MANA RBM will forward all SUSARs within 7 days of identifying an SAE meeting the SUSAR criteria to Bayer Pharmacovigilance Department for darolutamide or Ra-223. Bayer Consumer Care AG will be notified by automatic email notification of any reported SAEs entered into the EDC. SUSARs related to enzalutamide will be reported directly to the FDA.

Bayer AG will be responsible for reporting relevant SUSARs to the competent authority, other applicable regulatory authorities, and participating Site Investigators, in accordance with International Conference on Harmonisation (ICH) guidelines, FDA regulations, and/or local regulatory requirements.

All SAEs will be reported by MANA RBM to the IRB and a final summary of all SAEs will be provided in the Clinical Study Report.

14.5.1 **Sponsor Assessment of Suspected Unexpected Serious Adverse Reactions**

Known as Suspected Unexpected Serious Adverse Reactions (SUSARs), these events suspected (by the Site Investigator or Sponsor) to be related to the study drug, are unexpected (not listed in the IB or USPI), and are serious (as defined by the protocol) and require expedient submission to relevant health authorities within 7 days (fatal or life-threatening event) or 15 days (all serious events), or as defined by law.

The Sponsor is responsible for final determination of whether a SAE is as “unexpected.” MANA RBM will forward all SUSARs for Ra-233 or darolutamide to Bayer Consumer Care AG. All Ra-223 SUSARs will be unblinded to treatment. MANA RBM will forward all SUSARs within 7 days of identifying an SAE meeting the SUSAR criteria.

Bayer AG will be responsible for reporting relevant SUSARs to the competent authority, other applicable regulatory authorities, and participating Site Investigators, in accordance with International Conference on Harmonisation (ICH) guidelines, FDA regulations, and/or local regulatory requirements.

14.5.2 Sponsor Reporting for Clinical Studies Under an Investigational New Drug Application

Any written IND Safety Reports will be submitted to the FDA by the MANA RBM. Copies will be provided by email to Bayer Consumer Care AG.

15. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6(R2) Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

15.1 Institutional Review Board Approval

The clinical study protocol, ICF, patient documents (e.g., ePRO), patient recruitment procedures (e.g., advertisements), information about payments and compensation available to the patients, and documentation evidencing the Site Investigator's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The Site Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going IRB study review. The Site Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Site Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB. Safety updates for radium-223 and darolutamide will be prepared by the Bayer Consumer Care AG and distributed by MANA RBM to the Site Investigators and relevant IRB.

15.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

15.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.

An electronic informed consent (eConsent) will be used except in extenuating circumstances (e.g., if the internet is not functioning at the time the patient must sign the consent). The ICF, including translations, will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently

required by the FDA, as well as local county authority or state regulations and national requirements.

Before screening into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Site Investigator (or designee) is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A copy of the ICF, to include the patient's signature~~,~~ will be provided by the Site Investigator (or designee) to the patient.

Patients will be given the option to participate in the collection of biomarker samples for research. Patients can participate in the main study and opt out of the collection of biomarker samples for research. Patients can withdraw approval for participating in the research samples at any time. Patients can withdraw consent to main study or biorepository sampling, at any time. All data and documents collected between when the informed consent was signed by the patient and when the patient withdraws consent will remain in the study databases.

If an amendment to the protocol substantially alters the study design or the potential risks to patients, each ongoing patient's consent to continue participation in the study should be obtained.

15.4 Patient Confidentiality

Confidentiality of patient's personal data stored in the eISF or eSource limited-access sections containing protected health information (PHI) will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, as part of the informed consent process, the patient must sign an authorization form for the study that he or she has been informed of the following:

- What PHI will be collected from patients in this study
- Who will have access to that information and why?
- Who will use or disclose that information?
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the Site Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) during the Overall Survival phase of the study.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the Site Investigator and institution permit authorized representatives of the Sponsor, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include identification of subjects by using a unique subject ID that will identify patients in the eCRF or other documents submitted to the Sponsor. This information, together with the patient's year of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF portions that are accessible to non-site study personnel. No material bearing a patient's name or other PHI will be transmitted to Bayer Consumer Care AG. Patients will be informed of their rights within the ICF.

15.5 Site Investigator and Staff Information

Professional data of the Site Investigators and sub-Investigators may be included in the MANA RBM database and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Site Investigator or sub Investigator, MANA RBM shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

15.6 Financial Information

The finances for this clinical study will be subject to a separate written agreement between MANA Consulting LLC d/b/a MANA RBM, and/or CUSP and applicable parties. Any Site Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

16. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

16.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature-authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor. All amendments require review and approval of all pharmaceutical companies and the Study Lead-Principal Investigator supporting the study. The written amendment must be reviewed and approved by the Sponsor and submitted to the IRB at the Site Investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, or addition or removal of new tests or procedures, shall be reviewed and approved by the IRB of record for the Site Investigator's facility.
The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable, and IRB approval obtained, specifically when an increase to dosing or patient exposure and/or patient number has been proposed.

Items requiring a protocol amendment approval from IRB and/or FDA or other regulatory authorities include, but are not limited to, the following:

- Change to study design
- Increased risk to subjects
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition of tests and/or procedures

It should be further noted that if an amendment to the protocol substantially alters the study design or the potential risks to the patients as determined by the IRB, a revision to the ICF and their consent to continue participation in the study should be obtained.

16.2 Documentation Required to Initiate the Study

Before the study may begin certain documentation required by FDA regulations and ICH GCP must be provided by the Site Investigator. The required documentation will be provided in electronic format or as certified electronic documents and stored in the Site's electronic Investigator Site File (eISF)
Documents required to begin a study in the US include, but are not limited to, at a minimum, the following:

- A signed protocol signature page and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current curricula vitae for the Site Investigator and any Sub-Investigator(s) who will be involved in the study
- Appropriate nuclear medicine licensing
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB-approved consent form (and patient information sheet, if applicable) containing permission for audit by representatives of MANA RBM, the IRB, and the FDA and other regulatory agencies (as applicable)
- Financial disclosure forms for all Site Investigators listed on Form FDA 1572
- Site qualification reports, where applicable
- Verification of Site Investigator acceptability from local and/or national debarment list(s)

16.3 Study Documentation and Storage

All documents for the trial will be stored in an electronic Investigator Site File or electronic Trial Master File.

Documentation of staff associated with the trial, training, delegation of duties, and access to all electronic systems will be collected electronically using the Site Tracker Analyzing Risk (STAR database).

All data collected de novo for the trial will be entered directly into the electronic source system (eSource) using the principles of ALCOA (attributable, legible, contemporaneous, original, and accurate). The entry of subject data contemporaneous with subject visits aligns with the FDA Guidance on electronic Source and ICHE6(2).

Source documents such as medical history, lab reports, and other documents needed to confirm inclusion criteria, safety, or efficacy that reside in another location may be uploaded as certified electronic copies and stored in the PHI protected section of the eISF, available only to the Site and individuals identified in the Informed Consent.

The eISF should will contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57.

Drug accountability records will be collected electronically and will contain information regarding receipt, dosing, lot number, and disposition. They will be archived in the site's eISF.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation/records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Site Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Site Investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRFs, medical records). Informed consents will be collected electronically and will be archived in the eISF. The documents listed above must be retained by the Site Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval).

If the Site Investigator relocates, retires, or for any reason withdraws from the study, both the Sponsor and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Site Investigator, another institution, or to the Sponsor. All study files will be maintained by the Sponsor throughout the study and will be transferred to Bayer Consumer Care AG at the conclusion of the study. Note any patient-related

data containing PHI will only be stored in the eISF and will not be provided to Bayer Consumer Care AG.

16.4 Data Collection

The study eCRF is the primary data collection instrument for the study. The eCRF, and all data collection tools are validated. Systems and processes align with 21 CFR Part 11. Case report forms will be completed using the English language. For data collected *de novo* for the study will be entered as direct data capture. Patient reported outcomes, cognitive testing, and informed consents will be provided in English and Spanish.

In order to maintain confidentiality, only subject ID and year of birth will identify the patient in the eCRF. All documents containing PHI will be stored as certified copies in a special restricted access section of the Site's electronic Investigator Site File or the site's protected portion of the eSource (EDC) system. Only individuals with the roles described in the informed consent and the Site staff will have access to the data and files containing PHI.

The Site Investigator may file a personal patient identification list (Subject IDs with corresponding patient identifiers) in the PHI section of the eISF to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

At the end of the study or at the end of a patient's participation, the Site Investigator will electronically sign and date the patient eCRF casebook indicating that the data in the eCRF has been reviewed and approved by the Site Investigator.

16.5 Study Monitoring, Auditing, and Inspecting

The study will be monitored using a remote Risk Based Monitoring Approach (MANA Method) as described in Appendix E.

The Site Investigator will permit study-related monitoring, quality audits, and inspections by the Sponsor or its representative(s), government regulatory authorities, and the IRB of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The Site Investigator will ensure the capability for inspections of applicable study-related facilities. The Site Investigator will ensure that the study monitor, or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

Participation as a Site Investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the Sponsor or its representative(s).

16.6 Quality Assurance and Quality Control

Each study site shall be required to have Table of Contents of Standard Operating Procedures to define and ensure quality assurance/control processes for study conduct, safety reporting, handling radiopharmaceutical, data generation and collection, recording of data/documentation

and reporting according to the protocol, GCP and any applicable local, national or international regulations.

16.7 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication strategy.

17. REFERENCES

Alibhai et al. 2010
Alibhai SM, Breunis H, Timilshina N, et al. Impact of androgen-deprivation therapy on cognitive function in men with nonmetastatic prostate cancer. J Clin Oncol. 2010;28: 5030-5037.

Armstrong et al. 2018
Armstrong AJ, Lin P, Higano CS et al. Prognostic Association of Prostate-specific Antigen Decline with Clinical Outcomes in Men with Metastatic Castration-resistant Prostate Cancer Treated with Enzalutamide in a Randomized Clinical Trial. Eur Urol Oncol 2018; https://doi.org/10.1016/j.euo.2018.11.005.

Beer et al. 2014
Beer TM, Armstrong AJ, Rathkopf D et al. Enzalutamide in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. Eur Urol. 2017; 71: 151–154.

Clopper et al. 1934
Clopper C and Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika 1934; 26: 404-413.

Ferlay et al. 2015
Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136: E359-86.

Flaig et al. 2016
Flaig TW, Potluri RC, Ng Y, et al. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. Cancer Med. 2016 Feb; 5(2): 182–191.

Hussain et al. 2018
Hussain M, Fizazi K, Saad F, et al. PROSPER: A phase 3, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) in men with nonmetastatic castration-resistant prostate cancer (M0 CRPC). J Clin Oncol. 2018;36: 3.

Jim et al. 2010
Jim HS, Small BJ, Patterson S, Salup R, Jacobsen PB. Cognitive impairment in men treated with luteinizing hormone-releasing hormone agonists for prostate cancer: a controlled comparison. Support Care Cancer. 2010;18: 21-27.

Joly et al. 2006
Joly F, Alibhai SM, Galica J, et al. Impact of androgen deprivation therapy on physical and cognitive function, as well as quality of life of patients with nonmetastatic prostate cancer. J Urol. 2006;176: 2443-2447.

McGinty et al. 2014
McGinty HL, Phillips KM, Jim HS, et al. Cognitive functioning in men receiving androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. Support Care Cancer. 2014;22: 2271-2280.

Nead et al. 2016
Nead KT, Gaskin G, Chester C, et al. Androgen Deprivation Therapy and Future Alzheimer's Disease Risk. J Clin Oncol. 2016;34: 566-571.

Parker et al. 2013
Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. New Engl J Med. 2013; 269: 213-223.

Ryan et al. 2011
Ryan CJ1, Shah S, Efstathiou E, et al. Phase II study of abiraterone acetate in chemotherapy-I metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. Clin Cancer Res. 2011; 17: 4854-4861.

Scher et al. 2012
Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367:1187-97

Scher et al. 2016
Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working group 3. J Clin Oncol. 2016; 34: 1402-1418.

Shore et al. 2016
Shore ND, Chowdhury S, Villers A, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomized, double-blind, phase 2 study. Lancet Oncol. 2016; 17: 153-163.

Smith et al. 2019
Matthew Smith, Chris Parker, Fred Saad, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019; 20: 408–19

Tannock et al. 2014
Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004: 351:1502-1512.

Tran et al. 2009
Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science. 2009; 324: 787-790.

Wefel et al. 2011
Wefel JS, Vardy J, Ahles T, et al. International Cognition and Cancer Task Force Recommendations to Harmonise Studies of Cognitive Function in Patients with Cancer. Lancet Oncology. 2011; 12:703-708.

Nubeqa (darolutamide) [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 7/2019.

Xofigo (radium Ra 223 dichloride) [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 8/2018.

Xtandi (enzalutamide) [package insert]. Northbrook, IL: Astellas Pharma US, Inc; 7/2018.

18. APPENDICES

Appendix A: ECOG Performance Status Criteria

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

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

FACT-Cognitive Function (Version 3)

Below is a list of statements that other people with your condition have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PERCEIVED COGNITIVE IMPAIRMENTS	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogA1	I have had trouble forming thoughts	0	1	2	3	4
CogA3	My thinking has been slow	0	1	2	3	4
CogC7	I have had trouble concentrating	0	1	2	3	4
CogM9	I have had trouble finding my way to a familiar place	0	1	2	3	4
CogM10	I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
CogM12	I have had trouble remembering new information, like phone numbers or simple instructions	0	1	2	3	4
CogV13	I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
CogV15	I have had trouble finding the right word(s) to express myself	0	1	2	3	4
CogV16	I have used the wrong word when I referred to an object	0	1	2	3	4
CogV17b	I have had trouble saying what I mean in conversations with others	0	1	2	3	4
CogF19	I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4
CogF23	I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
CogF24	I have forgotten names of people soon after being introduced	0	1	2	3	4

FACT-Cog (Version 3)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogF25	My reactions in everyday situations have been slow.....	0	1	2	3	4
CogC31	I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
CogC32	My thinking has been slower than usual	0	1	2	3	4
CogC33a	I have had to work harder than usual to express myself clearly	0	1	2	3	4
CogC33c	I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
CogMT1	I have trouble keeping track of what I am doing if I am interrupted.....	0	1	2	3	4
CogMT2	I have trouble shifting back and forth between different activities that require thinking	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>COMMENTS FROM OTHERS</u>	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogO1	Other people have told me I seemed to have trouble <u>remembering information</u>	0	1	2	3	4
CogO2	Other people have told me I seemed to have trouble <u>speaking clearly</u>	0	1	2	3	4
CogO3	Other people have told me I seemed to have trouble <u>thinking clearly</u>	0	1	2	3	4
CogO4	Other people have told me I seemed <u>confused</u>	0	1	2	3	4

FACT-Cog (Version 3)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	PERCEIVED COGNITIVE ABILITIES	Not at all	A little bit	Some-what	Quite a bit	Very much
Cog PC1	I have been able to concentrate	0	1	2	3	4
Cog PV1	I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
Cog PM1	I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4
Cog PM2	I have been able to remember to do things, like take medicine or buy something I needed	0	1	2	3	4
Cog PF1	I am able to pay attention and keep track of what I am doing without extra effort	0	1	2	3	4
Cog PCH 1	My mind is as sharp as it has always been	0	1	2	3	4
Cog PCH 2	My memory is as good as it has always been	0	1	2	3	4
Cog PMT 1	I am able to shift back and forth between two activities that require thinking	0	1	2	3	4
Cog PMT 2	I am able to keep track of what I am doing, even if I am interrupted	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	IMPACT ON QUALITY OF LIFE	Not at all	A little bit	Some-what	Quite a bit	Very much
CogQ35	I have been upset about these problems	0	1	2	3	4
CogQ37	These problems have interfered with my ability to work	0	1	2	3	4
CogQ38	These problems have interfered with my ability to do things I enjoy	0	1	2	3	4
CogQ41	These problems have interfered with the quality of my life	0	1	2	3	4

ASSESSMENT

Timed Up & Go (TUG)

Patient _____

Date _____

Time _____ ☐ AM ☐ PM

Purpose: To assess mobility

Equipment: A stopwatch

Directions: Patients wear their regular footwear and can use a walking aid, if needed. Begin by having the patient sit back in a standard arm chair and identify a line 3 meters, or 10 feet away, on the floor.

NOTE: Always stay by the patient for safety.

① Instruct the patient:

When I say "Go," I want you to:

1. Stand up from the chair.
2. Walk to the line on the floor at your normal pace.
3. Turn.
4. Walk back to the chair at your normal pace.
5. Sit down again.

② On the word "Go," begin timing.

③ Stop timing after patient sits back down.

④ Record time.

Time in Seconds: _____

An older adult who takes ≥12 seconds to complete the TUG is at risk for falling.

OBSERVATIONS

Observe the patient's postural stability, gait, stride length, and sway.

Check all that apply:

- ☐ Slow tentative pace
- ☐ Loss of balance
- ☐ Short strides
- ☐ Little or no arm swing
- ☐ Steadying self on walls
- ☐ Shuffling
- ☐ En bloc turning
- ☐ Not using assistive device properly

These changes may signify neurological problems that require further evaluation.

CDC's STEADI tools and resources can help you screen, assess, and intervene to reduce your patient's fall risk. For more information, visit www.cdc.gov/steadi

CDC **Centers for Disease Control and Prevention** National Center for Injury Prevention and Control

2017

STEADI Stopping Elderly Accidents, Deaths & Injuries

Appendix B: Guidelines for Fertile Male Patients

Fertile male patients, defined as all males physiologically capable of conceiving offspring with female partners of child-bearing potential, must use condoms plus spermicidal agent during the study treatment period and for 3 months after the last dose of Ra-223/Placebo, and should not father a child during this period.

Male patients must also refrain from donating sperm during their participation in the study and for 3 months after the last dose of study drug.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

Appendix C: Schedule of Assessments

Open-Label Period Assessments	**Screening**	**R1**	**Lead-in RT1 (Day 1)**		**Lead-in RT1 (Day 28)**	**Lead-in RT1 (Day 56)**	**Lead-in RT1 (Day 84)**	**Pre-R2[a]**		**R2**
	-42 to -2 days prior to R1		*After R1 and before 1st dose of RT1*		*28 days +/- 7 days from Day 1*	*56 days +/- 7 days from Day 1*	*84 days + 7 days from Day 1*	*At 12-16 weeks after starting RT1*	*Final I/E review completed at least 48 hours prior to R2*	
Tests and Observations										
Informed Consent	X									
I/E Review (to be completed at least 48 hours prior to each randomization).	X								Review Inc. #12-15.	
Demographics	X									
Medical History	X									
Prostate Cancer History	X									
Physical Exam (PE)	X									
Abbreviated PE								X		
Vital Signs[b]	X							X		
Adverse Event Evaluation	X		X		X	X	X	X		
Relevant Prior Medication Review[w]	X									
Concomitant Medication Review	X							X		
Randomization(s)		X[s]								X[s]
Bone Fracture Risk Assessment[c]	X									
CANTAB Practice	X[u]									
CANTAB Assessments[x]			X[t]					X		
TUG (timed up and go)			X[t]					X		
ECOG PS	X		X[t]					X		
FACT-P			X[t]					X		
FACT-COG			X[t]					X		
12-lead ECG	X							X		
Use of other anti-cancer therapies								X		

Open-Label Period Assessments	**Screening**	**R1**	**Lead-in RT1 (Day 1)**		**Lead-in RT1 (Day 28)**	**Lead-in RT1 (Day 56)**	**Lead-in RT1 (Day 84)**	**Pre-R2[a]**		**R2**
	-42 to -2 days prior to R1		*After R1 and before 1st dose of RT1*		*28 days +/- 7 days from Day 1*	*56 days +/- 7 days from Day 1*	*84 days + 7 days from Day 1*	*At 84-112 days after starting RT1*	*Final I/E review completed at least 48 hours prior to R2*	
Lab Observations										
CBC, 3-part differential, and platelets[d,aa]	X							X	Review Inc. 15	
CMP[e,aa]	X							X	Review Inc. 15	
PSA[aa]	X		X[o]		X[o]	X[o]	X[o]	X	Review Inc. 12	
LDH[aa]	X							X		
ALP[aa]	X							X		
Research Biomarkers[q,aa] *(Optional consent)*	X							X		
Treatments										
Bone Health Agent administration[t]	X							X	Review Inc. 14	
All subjects : Write Enza prescription/and begin insurance qualification	X									
Enza Compliance (or) Daro Dispensing/ Accountability			X	X	X	X	X	X	Review Inc. 14	X
Staging										
CT or MRI Scan of the chest/ abdomen/pelvis[f]	X							X[p]	Review Inc. 13	
MRI or CT scan of the brain[g]	X									
Bone Scan[f]	X							X[p]		
RECIST Assessment								X[ac]	Review Inc. 13	
PCWG3 Assessment	X[ac]							X[ac]		
Bone fractures[h]			X		X	X	X	X		
Symptomatic Skeletal Events			X		X	X	X	X		

Double-Blind Period Assessments	**RT2 Cycles 1-6** ***Q28 days ±7 days, from previous dose[n]***	**RT2 Imaging** ***Q12 weeks ±1 week, from C1D1 through Cycle 6, or until Q12 week Prog FU***	**Telephone End of Study Drug[i]**	**Q12-Week Progression Follow-up[j]** ***Q12 weeks ±1 week***	**Overall Survival[k]** ***Q24 weeks ±4 weeks***	**End of Study** ***At time of Permanent Study DC***
Tests and Observations						
Abbrev. Physical Exam	X[ab]					
Vital Signs[b]	X			X		
Adverse Event Evaluation	X	X	X	X[l]	X[l]	X[l]
Concomitant Medication Review	X		X	X		
SSE Assessment	X		X	X	X	
Survival Status				X	X	X
TUG (timed up and go)				X[z]		
ECOG PS	X			X[z]		
12-lead ECG				X[z]		
RECIST and PCWG3 assessment		X		X		
Bone fractures and AESI assessment[h]	X	X		X	X	
Use of other anti-cancer therapies	X		X	X	X	

Double-Blind Period Assessments	**RT2 Cycles 1-6** ***Q28 days ±7 days, from previous dose[n]***	**RT2 Imaging** ***Q12 weeks ±1 week, from C1D1***	**End of Study Drug[i]**	**Q12-Week Progression Follow-up[j]** ***Q12 weeks ±1 week***	**Overall Survival[k]** ***Q24 weeks ±4 weeks***	**End of Study** ***At time of Permanent Study DC***
Laboratory Observations						
CBC, 3-part differential, and platelets[d]	X[y]			X		
CMP[e]	X[y]			X		
PSA	X[y]			X		
LDH	X[y]			X		
ALP	X[y]			X		
Research Biomarkers[q] *(Optional consent)*	X			X		
Treatments						
Enza Compliance (or) Daro Dispensing/ Accountability	X[m]			X[m]	X[m]	
RT2 : Ra-223 or Placebo	X[n]					
Staging						
CT or MRI Scan of the chest/ abdomen/pelvis[f]		X		X		
Bone Scan[f]		X		X		
Final Assessments						
Reason for Discontinuation						X
Study Disposition						X
Public Records Search						X

Appendix C: Schedule of Assessments (continued)

a Only done if ≥ 30% PSA decline during the initial 12 weeks of RT1 exposure.
b Vital signs will include height (first visit only), weight, resting heart rate, blood pressure, respiratory rate, and oral temperature)
c The bone fracture risk assessment includes a history of prior fractures, comorbidities, history of androgen deprivation therapy, history of prior bisphosphonate/denosumab use, prior bone density assessment (most recent bone density assessment prior to screening), and any relevant prior and ongoing medications.
d CBC includes hemoglobin, hematocrit, white blood cell (WBC) with 3-part differential and platelets. It must be done within 14 days prior to each Ra-223 cycle to determine safety of proceeding with each cycle.
e CMP will include measurements of glucose, blood urea nitrogen (BUN), creatinine, estimated creatinine clearance (Cockcroft-Gault), sodium, potassium, chloride, calcium, carbon dioxide (CO2), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total protein, and albumin. CMP may be done up to 14 days prior to RT2 cycles.
f A Screening CT or MRI scan (of the chest, abdomen, and pelvis) and bone scan will be performed within 42 days prior to Lead-In RT1 therapy. After Cycle 1, Day 1 (C1D1), assessments will occur every 12 weeks (+/- 7 days) after C1D1 irrespective of treatment delays, and will continue until the patient experiences radiological progression or initiates a prohibited treatment. All radiographic scans (CT, MRI and bone scans) will be collected and held by MANA RBM.
g MRI or CT scan of the brain ≤4 weeks required at screening only if clinically indicated
h Patients will be followed for all bone fractures throughout the course of the study.
i Patients should visit the site 30 days (±7 days) after the last dose of radium-223/placebo and 30 days (±7 days) after the last dose of enzalutamide/darolutamide. Patients must be followed for all AEs/AESI's for 30 calendar days after the last dose of radium-223/placebo and enzalutamide/darolutamide irrespective of the visit date.
j Patients who discontinue Ra-223 randomized treatment prior to progression or starting prohibited treatment will have progression follow-up visits every 12 weeks (±7 days) according to their original radiology schedule to determine disease progression. Patients enter Overall Survival Follow-up after documented radiological progression or initiation of a prohibited treatment.
k Patients will be followed every 6 months (±1 month) after the last Q12-Week Imaging Visit is performed (during randomized treatment or during follow-up) for survival status (e.g., date and cause of death) until the required number of events have been reached in the study or death, whichever occurs first. Provider or telephone visits are allowed.
l Only adverse events identified by the site investigator as SSE-related AEs, and Adverse Events of Special Interest (Section 14.1.2, 14.2.2) are to be reported after the end of Study drug treatment assessment.
m RT1 will be taken during the 12 weeks prior to RT2 randomization and continue to be taken throughout the 6 cycles of RT2 treatment and thereafter. Post Ra-223 or placebo, patients may continue to receive RT1 until no longer clinically beneficial or until contraindicated.
n C1D1 must occur ≤14 days after RT2 randomization. Ideally, radium-223 or placebo should be administered every 28 days (+/- 7 days) from the preceding dose after the C1D1. Subsequent cycles must be within >3 weeks and <8 weeks from last cycle. Delays are allowed to manage treatment-limiting toxicities or other limitations. Safety assessments needed before each cycle should be done within 14 days of the next cycle.
o PSA will be monitored every 28 days (+/- 7 days) from RT1 initiation during the 84-day (12 week) lead-in phase of the study.
p Scans will be done at Pre-R2 ONLY for patients who demonstrate ≥ 30% PSA decline during the initial 12 weeks of RT1 exposure. Window for obtaining repeat scans is within 28 days prior to RT2 randomization.
q If consented to optional research blood biomarkers, optional samples may be collected at screening (Pre-RT1), Pre-R2, and at the time of radiological progression or prior to initiating a prohibited treatment, whichever occurs earlier.
r Laboratory assessments do not need to be repeated on Cycle 1 Day 1 if performed within the prior 14 days. Labs may be collected up to 14 calendar days prior to Ra-223 cycles.
s R1 randomization is only done after all inclusion/exclusion criteria are satisfied. R2 randomization is only done if all (4) R2 randomization conditions are met.
t To be completed before taking first dose of enzalutamide or darolutamide.
u Cantab and ePRO practice to be done at screening to familiarize the patient with the iPad technologies used, and with testing instructions.
w Prior anticancer/relevant medication and procedure history review- including history of androgen deprivation therapy, orchiectomy, history of prior bisphosphonate/ denosumab use, vitamin D, calcium, anticancer medications, and exclusionary medications
x A battery of CANTAB Cognitive Function Tests.
y Repeat Labs are not needed for Cycle 1, Day 1, if they were drawn at Pre-R2 visit within 14 days of C1D1.
z Should be performed Q48 weeks after C1D1.
aa Should be done </= 14 days prior to Lead-in RT1 visit
ab Only required at C4D1.
ac Screening PCWG3 and Pre-R2 RECIST/PWG3 may be done any time prior to first Q12Week imaging visit. Only required to be done if ALL inclusion and exclusion criteria are met and subject is randomized to Ra-223 or Placebo.

Appendix D: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and PCWG3 Bone Progression

Definitions

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al 2009). Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Baseline Eligibility

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT (CT scan slice thickness no greater than 5 mm). • 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). • 20 mm by chest x-ray. **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10- to <15-mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, and abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
Target Lesions:	The most reproducible measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion or a short axis of ≥15 mm by CT scan. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.

Non-Target Lesions:	All other lesions should be identified as non-target lesions at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment, as per protocol screening requirements. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest X-ray:	Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, a CT scan is preferable.
Conventional CT and MRI:	CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).
Ultrasound:	When the primary study endpoint is objective response, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Therefore, use of these techniques for objective tumor response should be restricted to validation purposes in specialized centers. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers alone cannot be used to assess response. If markers are initially above the upper limit of normal, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
Cytology and Histology:	Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Response Criteria

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of diameters since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes must be non-pathological in size (<<10 mm short axis).
Stable Disease (SD):	Persistence of one or more non-target lesions and/or persistence of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. When the patient also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Evaluation of Best Overall Response

As detailed above, the best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required for studies in which response rate is the primary endpoint, but is not required in randomized studies or studies with primary survival endpoints (i.e., where response is not a primary endpoint).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	NO	CR
CR	SD	NO	PR
CR	NE	NO	PR
PR	SD OR NE	NO	PR
SD	SD OR NE	NO	SD
PD	ANY	YES OR NO	PD

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
ANY	PD	YES OR NO	PD
ANY	ANY	YES	PD

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy to confirm the CR status.
When nodal disease is included in the sum of target lesions, and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression, should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the eCRF.

PCWG3 Bone Scan Disease Progression Criteria (Scher et al. 2016)

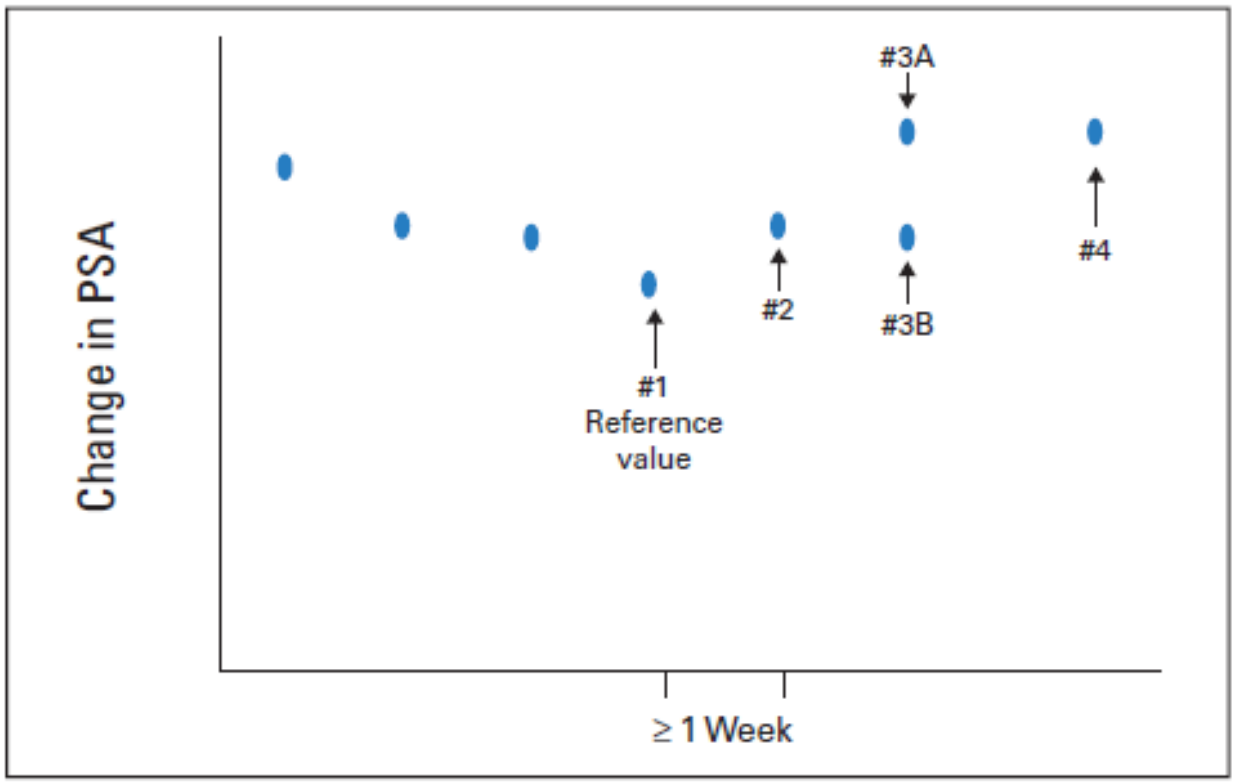
Appearance of 2 or more new lesions on bone scan, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions (2+2 rule). The date of progression is the date of the first scan that shows the change.

Or

Soft tissue disease progression by modified RECIST v1.1 to report changes in lymph nodes that were ≥ 2 cm in diameter at baseline with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later.

Note that for some treatments, a lesion may increase in size before it decreases.

PSA Progression Criteria



For eligibility based on prostate-specific antigen (PSA) changes (Inc #7a) use the diagram above for guidance on how to determine if the criterion "series of rising PSA" has been met. "Series" will refer to more than 1 rising value.

For the purposes of this protocol, the reference value (#1) will be the nadir PSA (1st PSA), with subsequent values obtained a minimum of 1 week apart. In the diagram above, #2 (2nd PSA) represents an example of the first increase in PSA after nadir. If the 3rd PSA (example #3A) is greater than #2, and total rise from nadir is >1 ng/mL, then eligibility has been met.

If the 3rd PSA (example #3B) is not higher than #2, but value #4 is, the patient is eligible if #4 is 1 ng/mL or higher than nadir PSA (#1).

Appendix E: Remote Risk Based Monitoring and Trial Management (MANA Method)

All data and essential documents are collected electronically directly or converted to certified electronic copies. Data and documents are reviewed remotely using the following methodology:

1. Risk Assessment- the study team will conduct a Risk Assessment to identify the errors that matter (i.e., errors that affect primary endpoints, human subject protection, subject safety, GCP, and investigational product management). Each risk is categorized by Impact, Likelihood of Occurring, and Ability to Detect. A risk score is derived for each risk. For risks with a score of 75 or above, an oversight approach, usually an analytic report, is developed to monitor those risks.
2. Assuring data sources for all errors that matter: the study team will review all data needed to perform Errors that Matter Analytics and will assure that the data are collected in one of the electronic systems. Usually the data will be captured in the EDC, Site Tracker Analyzing Risk Database (STAR Database), or REACHER, but other data sources may be used to collect the critical data needed for the analysis of Errors that Matter
3. Developing Errors that Matter Analytics—following identification of all high risks (score of 75 or above) and major deviations that affect analysis or subject safety, study specific analytic reports are designed, programmed, and validated. The analytic reports are listed in the Study Report Specifications Document. The number of the report is mapped to the Risk Assessment to provide traceability between the Risk and Oversight.
4. Automating complex analytics--Complex analytics are automated through REACHER™, the MANA RBM clinical quality management system. This set up includes designing workflow and decision support notifications that result from the analytics. Additional oversight reports are also developed in JReview including the Subject Profile Analyzing Risk (SPAR™), which provides a comprehensive subject specific view of critical data for efficacy and safety data across all timepoints, normalized to first date of treatment.
5. Developing Data and Document Review Guidelines (DDRG)—The data and document review guidelines map the review of all critical data and documents by reviewer and report number. The DDRGs define the review by all oversight members, regardless of role (e.g., data reviewer, site monitor, central monitor, medical monitor). The frequency of review is included in the DDRG. Confirmation of critical data for recruitment or efficacy may be confirmed by a comparison of certified copies of document when compared to data entered in the data collectors, but traditional SDV or page by page eCRF review is not performed.
6. Training of study team members is performed following completion of analytic reports and the DDRGs. It includes training on the data collection system specific for the trial and all reports that will be used for oversight by each role.
7. Review of data for errors that matter is conducted independent of the EDC using REACHER analytic reports or JReview, which combine data across databases.

Review of documents is conducted in the eTMF/eISF. Documentation of review is completed in the Site Tracker Analyzing Risk Database (STAR) or REACHER.

8. Trend analysis--Monthly the central monitor and lead data manager review all trends in errors that matter, issues, major deviations, screening, reason for screen failure, reason for early termination, site performance, reviewer performance, query topics, and document review. Trends are reviewed with the Site Monitor who provides feedback monthly to the Site Investigators and Study Coordinators.