City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010

Dept. of Radiation Oncology

TITLE: A Phase 2 Trial of Radium Ra 223 Dichloride in Combination with Androgen Deprivation Therapy and Stereotactic Body Radiation Therapy for Patients with Oligometastatic Castration-Sensitive Prostate Cancer (SHARP)

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STAGE (if applicable): N/A
MODALITY: Hormone therapy and radiation therapy
PHASE/TYPE: Phase 2

PRINCIPAL INVESTIGATOR: Savita Dandapani, M.D.
Ph: (626)-256-4673 ext 82247
Email: sdandapani@coh.org

CO-INVESTIGATOR(S): Tanya Dorff, MD
Kun Qing, PhD

PARTICIPATING CLINICIANS: Jeffrey Wong, MD, Sagus Sampath, MD, Dave Yamauchi, MD, Sumanta Pal, MD, Scott Glaser, MD, Julie Ressler, MD, Yi-Jen Chen, MD

BIO-STATISTICIAN: Paul Frankel, Ph.D.

PARTICIPATING SITES: City of Hope, Duarte, CA

City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010

Clinical Trial Protocol

A Phase 2 Trial of Radium Ra 223 Dichloride in Combination with Androgen Deprivation Therapy and Stereotactic Body Radiation Therapy for Patients with Oligometastatic Castration Sensitive Prostate Cancer (SHARP)

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Principal Investigator
Savita Dandapani, MD., PhD.
City of Hope National Medical Center
Dept. of Radiation Oncology
T:626-301-8247 x 82071
Email:sdandapani@coh.org

PROTOCOL TEAM

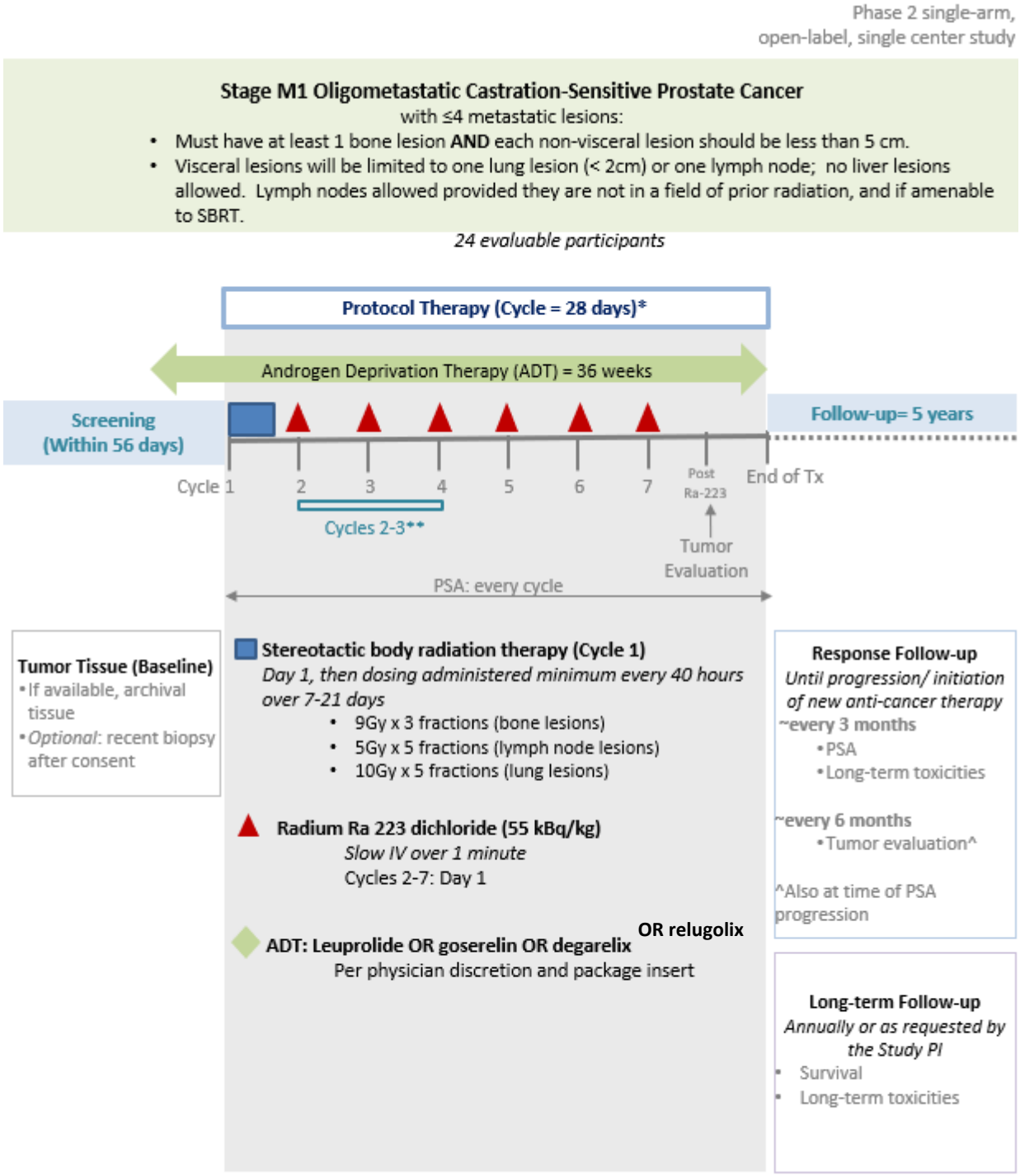
Biostatistician

Paul Frankel, PhD
Dept. of Information Sciences
T: 626-256-4673, x65265
Email:pfrankel@coh.org

Co-Investigator

Tanya Dorff, MD
Dept. of Medical Oncology
T:626-301-8247 x 89200
Email:tdorff@coh.org

EXPERIMENTAL DESIGN SCHEMA



*Protocol therapy lasts for 7 cycles of therapy/completion of ADT, until unacceptable toxicities or disease progression, whichever comes first.
** Stopping rules will be implemented after 2 cycles of radium 223 dichloride if unacceptable toxicity rate is ≥ 33%.

PROTOCOL SYNOPSIS

Protocol Title

A Phase 2 Trial of Radium Ra 223 Dichloride in Combination with Androgen Deprivation Therapy and Stereotactic Body Radiation Therapy for Patients with Oligometastatic Castration Sensitive Prostate Cancer (SHARP)

Study Detail

Population/Indication(s):	Prostate adenocarcinoma
Phase:	Phase 2
Sample Size:	24 evaluable patients
Estimated Accrual Duration:	48 months
Estimated Study Duration	~8 years
Participant Duration:	68 months (~8 months of treatment + 60 months follow-up)
Participating Sites:	City of Hope Duarte, CA
Study Agents:	Androgen deprivation therapy, radium Ra 223 dichloride, stereotactic body radiation therapy
Sponsor:	City of Hope
Industry Partner:	Bayer
Industry Partner Protocol Number:	IIR-US-2016-1801

Rationale for this Study

Carcinoma of the prostate remains a significant health problem in the United States, with 181,000 new cases and 26,120 deaths estimated in 2016[1]. Despite progress in early detection thanks to the widespread use of serum Prostate Specific Antigen (PSA) about 15 % of patients present with metastatic disease at diagnosis and 30 % of patients suffer eventual relapse to regional lymph nodes or distant organs despite local therapy. Historically several hypotheses based on clinical evidence attempted to explain mechanisms of metastatic tumor cell spread. Halsted suggested that tumors spread in an orderly manner initially spreading to regional lymph nodes and then centrifugally to distant organs[2]. In contrast the “systemic hypothesis” most clearly articulated by Fisher proposed two principal types of cancer: those that cannot metastasize and those that have metastasized widely before clinical detection[3]. In an attempt to reconcile clinical and laboratory features in a unified hypothesis, the “spectrum” model has been proposed[4]. This theory accepts that some tumors spread widely before clinical detectability while others never metastasize, but for the majority of cancers, metastatic capacity evolves during the clinical phase of tumor growth.

During the evolutionary process there may be a stage, termed “oligometastases”, when metastases are limited in number and location because metastatic capacity has not fully evolved[5].With a few exceptions such as testis cancer and some hematologic malignancies, the treatment of metastatic cancer by hormonal or cytotoxic agents is rarely curative and in many instances ineffective. In this context an important question is whether in the natural history of metastatic spread, there is a time when metastases are limited in number and/or in destination organs, and therefore treatment with systemic agents augmented by regional treatments may be effective. Examples of this include resection of lung metastases from sarcoma, liver metastases from colorectal cancer and isolated resection of breast metastases[6-8].

Despite its limitations hormone therapy and chemotherapy have been effective in eradicating subclinical deposits when used as an adjuvant to local therapy. But all too often the tumor recurs in a few locations, the likely consequence of the large number of tumor cells at these sites or limited drug availability at the site. These remaining oligometastases then may serve as a nidus for further dissemination. Metastatic prostate cancer is a heterogeneous disease and patients with ≤5 lesions have better survival than patients with > 5 metastatic lesions[9]. It is considered more likely that patients with limited number of metastases will benefit from local therapy to metastases and the patients with ≤ 4 metastases will be the focus of this proposed study. We have

previously reported results of a clinical trial in 29 patients with oligometastatic hormone sensitive prostate cancer treated at City of Hope with 36 weeks of androgen deprivation therapy and external beam radiation therapy (EBRT) up to 45 Gy to all (≤ 5) metastases[10]. We concluded that treatment with radiation therapy to oligometastases was feasible. 90% of patients treated with 36 weeks of ADT and EBRT to metastases achieved PSA nadir of <0.2 ng/mL that is known to be associated with good prognosis[11]. 4/8 patients with metastases limited to pelvic lymph nodes remained in remission off ADT after a median follow up of 25.7 months. We postulated that patients with oligometastases represent distinct subset of hormone sensitive prostate cancer that may serve as a focus for clinical trials evaluating novel local and systemic therapies in combination with ADT.

We hypothesize that it is possible and safe to treat patients with oligometastatic prostate cancer with even more aggressive regimen including: ADT, radium Ra 223 dichloride and SBRT to all known oligometastatic sites and that aggressive treatment of oligometastases(and bone micrometastases with radium Ra 223 dichloride early in the course of disease when disease is still sensitive to hormone manipulation will improve treatment outcomes of these patients and potentially delay disease progression and development of castration resistant phenotype. It is well known that bone is the most common site of micro and macrometastatic disease in prostate cancer and metastatic bone recurrence is present in 90% of patients with advanced prostate cancer and represents a significant site of treatment failure and source of morbidity and mortality[12].Therefore aggressive focus on the treatment of presumed micrometastatic bone disease underlies the hypothesis of early application of bone targeting with radium Ra 223 dichloride in our study. The proposed clinical trial builds upon our previous experience and expands the concept by introducing in this setting but also providing consolidation SBRT to known metastatic sites that will allow to deliver fully therapeutic doses of RT (versus sometimes palliative doses in the previous study).

Objectives

Primary Objective

- To assess the time to treatment failure (TTF) in patients who initiated the protocol regimen of androgen deprivation therapy (ADT) with stereotactic body radiation therapy (SBRT) and radium Ra 223 dichloride and received at least one dose with radium Ra 223 dichloride.

Secondary Objective

- To assess the safety of adding radium Ra 223 dichloride to SBRT and ADT in patients with oligometastatic castration sensitive prostate cancer.
- To assess the Prostate-Specific Antigen (PSA) and overall response rate (ORR) after 6 cycles of radium Ra 223 dichloride (Cycle 8 Day 1).
- To assess the progression-free survival (PFS) in patients with oligometastatic castration sensitive prostate cancer who initiated the protocol regimen of ADT with SBRT and radium Ra 223 dichloride and received at least one dose of radium Ra 223 dichloride.
- To assess time to bone specific PFS in patients with oligometastatic castration sensitive prostate cancer who initiated the protocol regimen of ADT with SBRT and radium Ra 223 dichloride and received at least one dose of radium Ra 223 dichloride.
- To assess overall survival, complete response rate, duration of response, and duration of overall complete response and duration of stable disease in patients with oligometastatic castration sensitive prostate cancer who initiated the protocol regimen of ADT with SBRT and radium Ra 223 dichloride.
- To assess long-term toxicities during 5-year follow-up in patients with oligometastatic castration sensitive prostate cancer who initiated the protocol regimen of ADT with SBRT and radium Ra 223 dichloride and received at least one dose of radium Ra 223 dichloride

Exploratory Objective

- To perform exploratory analysis of primary or metastatic tumor mutation patterns in this study population at baseline
- To identify immune system factors in the blood that change during the course of ADT-radiotherapy for metastatic prostate cancer
- To describe the rate of normalization of the total alkaline phosphatase level (defined as a return to a value within the normal range) at the end of protocol therapy in patients oligometastatic castration sensitive prostate cancer with total alkaline phosphatase values above the upper limit of the normal range at baseline
- To analyze the patients who were in consideration for the study and the reason for ineligibility, including radiographic review, PSA value, and treatment window.

Study Design

The SHARP study is a single-center open-label, Phase 2 clinical trial of stereotactic body radiation therapy (SBRT), hormone/androgen deprivation therapy (ADT) and radium Ra 223 dichloride for participants with metastatic castration sensitive prostate cancer.

Participants will initiate ADT (LHRH agonist leuprolide or goserelin, or LHRH antagonist degarelix or relugolix) for 4 weeks and then receive 32 weeks of ADT on protocol for a total of 36 weeks. Concurrent with standard of care ADT on protocol participants will receive 1 cycle of SBRT followed by 6 cycles of radium Ra 223 dichloride. SBRT is limited to ≤4 metastatic lesions with at least 1 bone lesion. Treatment cycles will be 28 days. Participants will receive bisphosphonate or RANKL inhibitor bone health agents at the dose and schedule consistent with the treatment of bone metastases or prevention of osteoporosis, starting approximately when the protocol therapy is initiated and ending when the patient reaches testosterone recovery (>50 ng/dL) or at the discretion of the PI.

Protocol therapy will last until completion of planned 8 cycles of therapy, unacceptable toxicity or progression, whichever comes first. If one agent is discontinued due to toxicity, then the participant may continue to receive the other protocol therapy agent(s).

Participants who end protocol therapy will undergo follow-upfor 5 years.

Evaluation Criteria and Endpoints

Response and progression will be evaluated in this study using modified Prostate Cancer Working Group 2 criteria. PSA levels will be a part of overall response assessment.

Efficacy Endpoints:

- Time to treatment failure
- Objective response rate
- Complete response rate
- Progression-free survival
- Bone specific progression-free survival
- Duration of response
- Duration of overall complete response
- Duration of stable disease
- Overall Survival

Toxicity

Toxicity will be recorded using the NCI CTCAE v 5.0.

Alkaline phosphatase

- Levels of alkaline phosphatase from baseline to end of study treatments

Statistical Considerations

With 24 evaluable patients treated we will estimate median time to treatment failure (radiographic or PSA progression, death or cessation of treatment due to clinical progression or toxicity). We seek to demonstrate a median TTF of at least 25 months, exceeding reports from all previous prior studies that examined only a two modality approach. With 24 evaluable patients, accrued over 16 months and followed for 18 months, we will have greater than 80% power to detect an improvement in TTF from 16 months to 32 months with a one-sided type I error of 10%. The critical value for a promising median TTF based on this design is 25 months, or an improvement of 9 months over our historical data.

Other secondary analysis will include progression-free survival, overall survival, complete response rate, duration of response, and duration of overall complete response, duration of stable disease and analysis of alkaline phosphatase levels.Exploratory analysiswill include evaluation of the role of genomic mutations and immune biomarker studies on outcome and toxicity. These outcomes will be reported to provide further support, combined with the activity, and tolerability to help guide additional studies.

Eligibility Criteria

Main Inclusion Criteria

- Adult patients with life expectancy > 12 months and ECOG ≤ 2
- Histologic diagnosis of prostate adenocarcinoma.
- Stage M1
- Up to 5 metastatic lesions:
- Must have at least 1 bone lesion **AND** each non-visceral lesion should be less than 5 cm
- Visceral lesions will be limited to one lung lesion (< 2cm) or one lymph node; no liver lesions allowed. Lymph nodes allowed provided they are not in a field of prior radiation, and if amenable to SBRT (to be reviewed by PI). (note: locoregional recurrence is not considered a “visceral metastatic lesion”. This is discussed more below)
- Two lesions can be in close proximity (i.e. within 5cm of each other) if they meet radiation SBRT normal tissue toxicity requirements
- *If have untreated primary prostate cancer*: Must undergo debulking prostatectomy at discretion of treating urologist or definitive radiation therapy. Definitive radiation fields to include close proximity lymph nodes at discretion of treating radiation oncologist. Definitive radiation dose at discretion of treating radiation oncologist.
- If had prior treatment to the prostate primary (definitive radiation therapy or prostatectomy, and can include salvage radiation to the prostate bed +/- lymph nodes), no evidence of locally persistent or recurrent prostate cancer on digital rectal exam (DRE) OR imaging studies (CT or MRI).
    - Note: patients with asymptomatic low volume locoregional recurrent disease will be allowed to enroll on this study after discussion with the PI. In the case where the low volume recurrence is amenable to SBRT, it will be included in the SBRT treatment. In the case where the low volume recurrence is not amenable to SBRT based on reirradiation risk, then we will follow these lesions with re-imaging scans and reassess at later time points for further local control. Additionally, if these patients fail only at the untreated site (due to the untreated recurrence not being amenable to SBRT) they will be censored in the primary efficacy analysis at that time.
- Does not have castration resistant disease (i.e. testosterone >50 ng/dl)

- PSA ≥0.2 prior to start of androgen deprivation treatment (ADT)
- Patients will be receiving approximately 36 weeks of ADT as part of this trial. The 36 weeks of ADT may start prior to consenting to this study. The patient may join the study at any point of the 36-week period of ADT treatment. .
- Patients must be willing to receive bisphosphonate or RANKL inhibitor bone health agents at the dose and schedule consistent with the treatment of bone metastases or prevention of osteoporosis, starting approximately from when the patient begins protocol therapy, until the patient's testosterone reaches normal levels or at the discretion of the PI. Patients who are already on a bone health agent separate from the protocol may continue on this treatment regimen and will not be required to start treatment with an additional bone health agent.
- May have received prior hormonal therapy at the discretion of the PI. Patients may have received prior targeted therapy in the context of definitive treatment of a primary tumor.
- Must have refused standard of care treatment for metastatic disease

Main Exclusion Criteria

- Prior Radium Ra 223 dichloride
- Prior or concomitant chemotherapy for metastatic or recurrent disease with the following **exceptions**:
    - Prior chemotherapy for local primary disease is permitted.
- Prior radiation treatment for metastatic disease is allowed provided that it is controlled and the total number of metastatic lesions does not exceed 5.
- Concomitant radiation treatment to primary prostate site
- Bilateral orchiectomy. If unilateral orchiectomy, eligible if testosterone >50 ng/dl.
- Metastases that in the judgment of investigator-radiologist are not amenable to SBRT

Investigational Product Dosage and Administration

Agent/Therapy and Route of Administration	Dose	Timing of administration and planned duration
Stereotactic Body Radiation Therapy (SBRT) via *External Beam Radiation via TrueBeam Stx*	9Gy x 3 fractions (bone) 5Gy x 5 fractions (lymph node) 10Gyx5 (lung)	**Cycle 1** Day 1, then dosing administered minimum every 40 hours over 7 to 21 days during Cycle 1
Radium Ra 223 dichloride via *Slow IV over 1 minute*	55 kBq/kg	**Cycles 2-7** Day 1 of each 28-day cycle
Leuprolide **OR** goserelin **OR** degarelix **OR** relugolix *Per package insert/ investigator discretion*		For a total of approximately 36 weeks. May start prior to consenting on study.

Clinical Observations and Tests to be Performed

- Medical history and physical exam
- Safety assessments (CBCs and comprehensive chemistry panel)
- PSA, serum alkaline phosphatase, serum testosterone
- CT/ MRI scans
- Correlative tumor tissue and blood

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ABBREVIATIONS

Abbreviation	Meaning
ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
CBC	Complete Blood Count
CFR	Code of Federal Regulation
CCP	Comprehensive Chemistry Panel
COH	City of Hope
CR	Complete response
CRA/CRC	Clinical Research Associate/Coordinator
CRF	Case Report Form
CSPC	Castration Senstitive Prostate Cancer
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
HER	Electronic Health Record
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HIPAA	The Health Insurance Portability and Accountability Act
HIV	Human immunedeficiency virus
IB	Investigator Brochure
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
LH	Luteinizing hormone
LHRH	Luteinizing hormone-releasing hormone
MRI	Magnetic resonance imaging
MRN	Medical record number
OCTAM	Office of Clinical Trials Auditing and Monitoring
OIDRA	Office of IND Development and Regulatory Affairs
ORR	Objective response rate
PC	Prostate Cancer
PD	Progressive Disease
PET-CT	Positron emission tomography–computed tomography
PFS	Progression-free survival
PHI	Protected health information
PI	Principal Investigator
PMT	Protocol Management Team
PR	Partial response
PSA	Prostate specific antigen
RR	Response rate
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiation Therapy
SD	Stable disease
TTF	Time to treatment failure
ULN	Upper limit of normal
UP	Unanticipated problem

1.0 OBJECTIVES

1.1 Primary Objectives

- To assess the time to treatment failure (TTF) in patients who initiated the protocol regimen of androgen deprivation therapy (ADT) with stereotactic body radiation therapy (SBRT) and radium Ra 223 dichloride and received at least one dose with radium Ra 223 dichloride.

1.2 Secondary Objectives

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- To perform exploratory analysis of primary or metastatic tumor mutation patterns in this study population at baseline
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- To analyze the patients who were in consideration for the study and the reason for ineligibility, including radiographic review, PSA value and treatment window.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Carcinoma of the prostate remains a significant health problem in the United States, with 181,000 new cases and 26,120 deaths estimated in 2016[1]. Despite progress in early detection thanks to the widespread use of serum Prostate Specific Antigen (PSA) about 15 % of patients present with metastatic disease at diagnosis and 30 % of patients suffer eventual relapse to regional lymph nodes or distant organs despite local therapy. Historically several hypotheses based on clinical evidence attempted to explain mechanisms of metastatic tumor cell spread. Halsted suggested that tumors spread in an orderly manner initially spreading to regional lymph nodes and then centrifugally to distant organs[2]. In contrast the "systemic hypothesis" most clearly articulated by Fisher proposed two principal types of cancer: those that cannot metastasize and those that have metastasized widely before clinical detection[3]. In an attempt to reconcile clinical and laboratory features in a unified hypothesis, the "spectrum" model has been proposed[4]. This theory accepts that some tumors spread widely before clinical detectability while others never metastasize, but for the majority of cancers, metastatic capacity evolves during the clinical phase of tumor growth.

During the evolutionary process there may be a stage, termed "oligometastases", when metastases are limited in number and location because metastatic capacity has not fully evolved[5]. With a few exceptions such as testis cancer and some hematologic malignancies, the treatment of metastatic cancer by hormonal or cytotoxic agents is rarely curative and in many instances ineffective. In this context an important question is whether in the natural history of metastatic spread, there is a time when metastases are limited in number and/or in destination organs, and therefore treatment with systemic agents augmented by regional treatments may be effective. Examples of this include resection of lung metastases from sarcoma, liver metastases from colorectal cancer and isolated resection of breast metastases[6-8].

Despite its limitations hormone therapy and chemotherapy have been effective in eradicating subclinical deposits when used as an adjuvant to local therapy. But all too often the tumor recurs in a few locations, the likely consequence of the large number of tumor cells at these sites or limited drug availability at the site. These remaining oligometastases then may serve as a nidus for further dissemination. Metastatic prostate cancer is a heterogeneous disease and patients with ≤5 lesions have better survival than patients with > 5 metastatic lesions[9]. It is considered more likely that patients with limited number of metastases will benefit from local therapy to metastases.

We have previously reported results of a clinical trial in 29 patients with oligometastatic hormone sensitive prostate cancer treated at City of Hope with 36 weeks of androgen deprivation therapy (ADT) and external beam radiation therapy (EBRT) up to 45 Gy to all (≤ 5) metastases[10]. We concluded that treatment with radiation therapy to oligometastases was feasible. Ninety percent of patients treated with 36 weeks of ADT and EBRT to metastases achieved PSA nadir of <0.2 ng/mL that is known to be associated with good prognosis[11]. Four of 8 patients with metastases limited to pelvic lymph nodes remained in remission off ADT after a median follow up of 25.7 months. We postulated that patients with oligometastases represent distinct subset of hormone sensitive prostate cancer that may serve as a focus for clinical trials evaluating novel local and systemic therapies in combination with ADT. In our current trial we are now allowing patients with lower PSA (i.e. PSA >0.2) due to recent advances in imaging to detect oligometastatic disease at lower PSA levels.[13]Similar PSA levels were used as inclusion criteria in the recently published oligometastatic STOMP trial[14, 15].

We hypothesize that it is possible and safe to treat patients with oligometastatic prostate cancer with even more aggressive regimen including: ADT, radium Ra 223 dichloride and SBRT to all known oligometastatic sites and that aggressive treatment of oligometastases(and bone micrometastases with radium Ra 223 dichloride) early in the course of disease when disease is still sensitive to hormone manipulation will improve treatment outcomes of these patients and potentially delay disease progression and development of castration resistant phenotype. It is well known that bone is the most common site of micro and macrometastatic disease in prostate cancer and metastatic bone recurrence is present in 90% of patients with advanced prostate cancer and represents a significant site of treatment failure and source of morbidity and mortality[12]. Therefore, aggressive focus on the treatment of presumed macrometastatic bone disease underlies the hypothesis of early application of bone targeting with radium Ra 223 dichloride in our study. The proposed clinical trial builds upon our previous experience, and expands the concept by introducing radium Ra 223 dichloride in this setting but also providing consolidation SBRT to known metastatic sites that will allow to deliver fully therapeutic doses of RT (versus sometimes palliative doses in the previous study)[10].

2.2 Hormone Therapy

Since testosterone is the main growth and survival factor for prostate cancer most patients will respond initially to ablation of gonadal androgen production through surgical (bilateral orchiectomy) or medical (luteinizing hormone-releasing hormone (LHRH) agonist or antagonist therapy [39]) approaches[16]. Unfortunately eventually all patients will develop progressive disease despite continued androgen suppression, with a median time to progression of 14 to 30 months[17].There are many mechanisms responsible for the development of resistance to androgen deprivation. They include amplification of androgen receptors, increased sensitivity of androgen receptors, mutations of androgen receptors that allow activation by non-androgenic ligands and activation of alternative survival pathways[18]. Recent data suggests that early application of docetaxel chemotherapy in addition to androgen suppression results in significant survival extension in patients with metastatic hormone sensitive prostate cancer, but this benefit appears to be particularly robust in patients with extensive metastatic disease and data for patients with oligometastatic disease (our study population) is not compelling[19].

Unfortunately once resistance to hormone therapy occurs, prognosis is dismal. This so-called castration resistant prostate cancer (CRPC) is characterized by virulent biologic and clinical behavior with median survival of 18-35 months[20]. Multiple life –extending agents have been approved in the last 10 years for the treatment of CRPC including immunotherapy (Sipuleucel-T), second generation androgen-pathway inhibitors (abiraterone, enzalutamide), chemotherapy (docetaxel, cabazitaxel) and radioactive isotope Radium Ra 223 dichloride[20]; however no significant therapeutic progress has been made in patients with hormone sensitive disease outside of subset with extensive metastases[19].

2.3 Radium Ra 223 Dichloride

Radium Ra 223 dichloride is an α emitting, bone seeking calcium-mimetic that selectively targets and binds to increased areas of bone turnover in bone metastases. The drug is administered by intravenous injection at four week intervals for a total of six injections.

2.3.1 Clinical experience

The ALSYMPCA trial was a randomized, double blind, Phase 3 study that compared six injections of radium Ra 223 dichloride against placebo in men with CRPC and bony metastases who had received, were not eligible to receive, or had declined docetaxel chemotherapy[21].Median overall survival was longer with

radium Ra 223 dichloride than placebo (14.9 *v* 11.3 months; hazard ratio 0.70, 0.58 to 0.83; P<0.001). Subsequent subgroup analysis showed a survival benefit with radium Ra 223 dichloride, irrespective of previous docetaxel use. In addition, a significant improvement in median time to first symptomatic skeletal event was seen for radium Ra 223 dichloride versus placebo (15.6 *v* 9.8 months; hazard ratio 0.66, 0.52 to0.83; P<0.001). Radium Ra 223 dichloride was well tolerated and associated with fewer adverse events than placebo. Although the difference was not significant, a slightly higher rate of diarrhea (25% *v* 15%) was seen with radium than with placebo. Other known side effects include nausea, vomiting, peripheral edema, and hematologic abnormalities (anemia, leukopenia, thrombocytopenia, neutropenia). It is notable that hematologic toxicities of Radium 223 were modest even in this population of patients with very advanced, and heavily pretreated disease. A meaningful improvement in quality of life was also noted for radium compared with placebo. The American Urological Association (AUA) guideline recommends radium Ra 223 dichloride for use in patients with CRPC with bony metastases, no known visceral metastases, and good performance status, irrespective of previous docetaxel use. Radium Ra 223 dichloride has always been used in conjunction with ongoing ADT therefore safety data for that combination is established.

2.4 Stereotactic radiation therapy

Stereotactic body radiation treatment (SBRT) for oligometastatic disease has emerged as a treatment modality to improve local control of metastases and delay need for toxic systemic treatment. There are numerous studies utilizing SBRT for oligometastatic patients with various histologies. For prostate in particular there have been a few recent papers documenting safety and efficacy of treating oligometastatic prostate cancer patients.

One such study from Philadelphia looked at the benefit of SBRT in patients heavily treated for metastatic prostate cancer[22]. 24 patients were treated and there was improved median survival (>3yrs vs. 11 months) for patients with ≤ 4 oligometastases. The radiation dose for SBRT was 24 Gy (18-50Gy) in 3 to 5 fractions (8Gy x 3). Most sites were bone and lymph nodes and toxicity was only reported in 2patients, one with grade 1 diarrhea and one with Grade 2 pelvic pain[22].

Another study from Belgium looked at benefit of SBRT for newly diagnosed oligometastatic patients[23]. Their dose was 50 Gy in 10 fractions (40-50Gy in 8-10 fractions, dose sculpted to respect normal tissue tolerances) for newly metastatic patients presenting with three synchronous oligometastases (bone and or lymph nodes). Berkovic *et al*.[23]demonstrated that SBRT was able to defer palliative androgen deprivation therapy for a median of 38 months and was safe with no Grade 3 toxicity observed.

Of note there are two ongoing multi-institutional trials using androgen deprivation and SBRT radiation for the bulk of the metastatic prostate cancer already but none thus far combining with xofigo to eradicate micrometastatic disease NRG BR001 A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases and STOMP surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence[24].In the multi-institutional NRG BR001 Phase 1 study, oligometastatic breast, lung, or prostate patients are eligible to receive radiation to ≤ 4 metastatic sites. For prostate in particular the continuation of androgen deprivation is allowed. The radiation doses are in the range of 10-15Gy per fraction for 3 to 5 days as compared to palliative radiation given in doses of 3Gy per fractions for 10 days. The Phase 1 portion of this trial for bone has already met accrual and results are pending.

In the STOMP trial, prostate patients with oligometastatic recurrence of prostate cancer are eligible to receive SBRT[24].The trial is limited to SBRT alone without concurrent systemic treatment. It is a randomized Phase 2 study to see if there is benefit of SBRT versus active surveillance of patients with

oligometastatic prostate cancer. The hypotheses is that patients treated with SBRT will have a longer ADT free survival and longer time to initiation of long term androgen deprivation use. The trial delineates radiation dose guidelines for lymph node and bone metastases. The dose is 10Gy x 3 fractions building from prior studies of this same groups utilizing this SBRT radiation dose with concomitant androgen deprivation therapy[24]. Toxicities from this SBRT regimen were mild and of 50 patients treated, only 10 patients had either Grade 1 or 2 toxicities[24]. The 50 patients had 70 metastatic lesions treated and local control of 100%; lesions included mostly bone and lymph nodes with only 2% visceral metastases; from 2005-2012 the dose was 50Gy in 10 fractions and from 2012-2014 the dose was 30Gy in 3 fractions. Our study is limiting to lymph node and bone metastases using similar radiation dose guidelines of both the STOMP trial and the NRG BR001 trial. The STOMP trial has now been published and demonstrated that SBRT to multiple metastatic sites (three or less) is safe and does delay metastatic progression and thus initiation of androgen deprivation therapy (ADT) (Ost et al 2018)[14]. The median ADT-free survival was 13 months for the observation/active surveillance group and 21 months for the metastasis-directed therapy group (either surgery, radiation or a combination)[14].

A recent National Cancer Database (NCDB) analysis of metastatic prostate cancer patients demonstrated that patients who received radiation to prostate primary had improved overall survival on both univariate and multivariate analysis[25]. On univariate analysis 5 year OS improved from 25% to 49% and 8yr OS estimates improved from 13% to 33%). Radiation dose over 65Gy was associated with improved overall survival consistent with reports of men with localized prostate cancer. Cho *et al.* [26]also demonstrated improved overall survival in metastatic prostate patients who received radiation to prostate primary in addition to ADT (3 yr OS increased from 43% to 69%) [26]. A large phase III trial of over 2000 patients, STAMPEDE, also showed improved survival with definitive radiation to the prostate primary in the subset of patients with limited metastatic disease (low burden metastatic burden) [27]. 3 year OS in this limited metastatic disease subset of STAMPEDE increased from 73% to 81% with HR of 0.68 (p value of .0098)[27]. In the STAMPEDE trial limited metastatic disease was defined as <4 bone metastases and no visceral metastases (i.e. lung, liver metastases) [27]. Lymph nodes were not included in the metastatic definition (i.e. visceral disease always recorded as nonnodal and in STAMPEDE over 60% had lymph nodes N+ disease) [27]. There has also been a recent abstract of adding definitive prostate radiation (74Gy to prostate, 60Gy to lymph nodes) concurrent with Ra-223 but no SBRT (ADRRAD trial); recent abstract shows this regimen to be safe and early promising results on whole body MRI [28]. Also in our predecessor trial IRB# 05190, approximately 50% of patients on the trial had definitive prostate radiation (+/- close proximity lymph nodes) [10, 29]. Due to the recent literature, recent change in NCCN and Via Oncology guidelines and that our predecessor trial allowed definitive prostate radiation we are now allowing definitive radiation to the prostate prior to cycle 1 of this trial.

Other earlier papers also analyzing large databases have demonstrated benefit of radical prostatectomy in men with metastatic prostate cancer[30-33]. We have been allowing radical prostatectomy prior to cycle 1 of this trial as well and will continue to allow patient choice of treatment for untreated prostate primary similar to our predecessor trial IRB #05190 [10, 29].

2.5 Bone Health Agents

To optimize treatment with androgen deprivation therapy, Ra-223 and SBRT, we must minimize risk of adverse events. In particular, non-pathologic fractures are an area of concern. Patients on this study are required to take bone health agents (BHAs) including bisphosphonates or RANKL inhibitors, from the start of protocol therapy (approximately) until the participant's testosterone levels are within the normal range or at the discretion of the PI.

The present study is a phase II trial on the use of Ra-223 with ADT and SBRT for metastatic castrate sensitive prostate cancer (mCSPC) patients. Each treatment agent on this study independently increases fracture risk. Ra-223 alone was shown to increase fracture risk in the REASURE study, a prospective trial on fracture risk in patients receiving Ra-223 monotherapy. For the Ra-223 cohort (n=36), 74 new fractures were identified in 20 patients (56%) at a median follow-up of 16.3 months, while for the reference cohort (n=36), 16 new fractures were identified in 12 patients (33%) at a median follow-up of 24 months [34]. Radiation therapy is also associated with a high incidence of fractures. A meta-analysis of 21 studies and 3929 patients with gynecologic cancers who received external beam radiation therapy found that pelvic insufficiency fractures occurred in 14% of patients, with 73.6% of fractures developing in the sacral bone or joint. The median time to fracture was 7.1 to 19 months post-radiation therapy [35]. The effect of ADT on fracture risk was described in a nationwide cohort study (n=144,670) in Korea, which showed that in patients with prostate cancer, ADT significantly increases the risk of newly developed fractures (HR, 1.815; 95% CI, 1.703–1.935; $p < 0.0001$) and osteoporosis (HR, 1.381; 95% CI, 1.305–1.461; $p < 0.0001$) compared to those not receiving ADT, and this is positively correlated with the duration of ADT [36].

Patients receiving androgen deprivation therapy (ADT) and Radium-223 (Ra-223) in combination face a significantly increased risk of non-pathological fractures. The phase 3 ERA 223 study on metastatic castrate resistant prostate cancer (mCRPC) patients was unblinded prematurely after an unplanned ad-hoc analysis revealed significantly increased fracture rates with the addition of Ra-223 to treatment with abiraterone acetate and prednisone or prednisolone. While fractures of any grade occurred in 11% of patients receiving a placebo instead of Ra-223, this increased to 29% of patients for the group receiving Ra-223 [37]. 78% of all fractures occurred at uninvolved sites, not metastatic sites.

BHAs have been shown to reduce the occurrence of fractures in this setting. On the ERA 223 study, the use of bone health agents (BHAs) was only allowed for patients who were on BHAs at baseline, which was around 40% of the study population. No patients were permitted to initiate BHA use while on study. They reported that in both the Ra-223 and placebo groups, patients on BHAs from baseline were associated with a lower fracture rate. For the Ra-223 group, fractures occurred in 15% of patients using BHAs, compared to 37% of patients not using BHAs. For the placebo group, fractures occurred in 7% of patients using BHAs, compared to 15% of patients not using BHAs [38].

After the ERA223 trial reported the increased risk of fractures with the addition of Ra-223, the EORTC1333/PEACE III trial was amended to mandate that all patients must start using a BHA. This trial compared enzalutamide and Ra-223 to enzalutamide alone for mCRPC patients, and reported that when Ra-223 is combined with enzalutamide treatment, the risk of fracture significantly increases from 13% to 33%. They found that when BHAs are used a minimum of 6 weeks before the first administration of Ra-223, this risk is almost abolished [39]. The results of these studies necessitate BHA use in our present study, as Ra-223, ADT and SBRT are used in a combined treatment regimen. The need for BHA use is clearly demonstrated for mCRPC patients treated with ADT and Ra-223. BHAs like bisphosphonates and RANKL inhibitors are also indicated for use in mCSPC patients on ADT to prevent treatment-induced bone loss and resulting fractures at a dosage of 60 mg denosumab every 6 months or 5 mg zoledronic acid once per year, respectively [40]. Patients on this study will be required to take bisphosphonates or RANKL inhibitors to reduce the risk of fracture associated with Ra-223, ADT and SBRT.

2.6 Overview and Rationale of Study Design

The SHARP study is a single-center open-label, Phase 2 clinical trial of stereotactic body radiation therapy (SBRT), hormone/androgen deprivation therapy (ADT) and radium Ra 223 dichloride for participants with newly diagnosed oligometastatic castration sensitive prostate cancer.

Eligibility

Participants will be adults diagnosed with metastatic prostate adenocarcinoma who have undergone full treatment at the primary prostate site. Participants will be chemotherapy naïve to metastatic sites, unless exposure occurred during treatment for primary disease.

Oligometastic burden will be limited to a maximum of four lesions, consistent with a summary analysis demonstrating improved prognosis for SBRT in prostate cancer for participants with four of fewer lesions [22]. In addition, participants must have at least one bone lesion to increase benefit over any risk from the bone specific radium Ra 223 dichloride regimen.

Participants must have at least one bone lesion and each non-visceral lesion (bone and lymph node) should not exceed more than 5 cm. In addition, participants may have one lung lesion (< 2cm); no liver lesions are permitted.

Treatment program

The treatment program is comprised of SBRT, administered over the first cycle, radium Ra 223 dichloride administered over 6 cycles, and concurrent standard of care ADT (luteinizing hormone-releasing hormone agonist-either leuprolide or goserelin, or LHRH antagonist degarelix or relugolix). Each treatment cycle is 28 days.

Participants will be receiving ADT for approximately 36 weeks as part of this study (can be started prior to consent) to increase radiosensitivity [23, 41]. Metastatic prostate cancer patients often present at COH having initiated standard of care ADT. Therefore, there is no benefit derived from monitoring patients during their initial single-agent standard of care ADT.

Typically standard of care ADT is continued indefinitely however it is associated with side effects of fatigue, hot flushes, erectile dysfunction, muscle loss, osteoporosis and sometime “drug holidays” are given. Thus, ADT will be discontinued after a total of 36 weeks and participants will be monitored carefully. We hypothesize that some patients may achieve long-term remission off ADT, however upon disease recurrence ADT (and other appropriate standard treatment) will be resumed.

Around initiation of protocol therapy, participants will also be required to take bisphosphonate or RANKL inhibitor bone health agents at the dose and schedule consistent with the treatment of bone metastases or prevention of osteoporosis. Participants will continue this regimen until they have reached testosterone recovery, or at the discretion of the PI.

SBRT

SBRT (dosing administered minimum every 40 hours from Day 1 over 7-21 days during Cycle 1). The dose of SBRT will be 9Gy x 3 fractions to bone metastases and 5Gy x 5 factions to lymph node metastases respecting normal tissues tolerances. Dose constraints will be similar to previous radiation therapy oncology group trials and multiple papers detailing stereotactic body radiation therapy (SBRT). Normal tissue constraints based on previous published multi-institutional trials and on the national physics guidelines set forth by AAPM task group 101 [42]. Primarily our dose constraints will be based on NRG-BR001 and previous published RTOG trials: RTOG 0236, 0813, 0915, 0438, 0613. These other RTOG trials

already looked at safe SBRT doses for lung, liver, spine and bone metastases. Per previous established SBRT protocols each separate oligometastatic site will have its own separate isocenter. Of note ongoing SBRT trial STOMP dose escalates to 10Gy x 3 fractions but does not allow for the concurrent use of ADT or include radium Ra 223 dichloride [24]. NRG BR001 also dose escalates based on tumor metastasis site from 10Gy x 3 fractions to 15Gy x 3 fractions or 10Gy x 5 fractions if central structures and allows concurrent use of ADT (NCT02206334). Other published studies have documented efficacy of 9Gy x 3 fractions and this is Dose Level -1 for the ongoing SBRT trials and thus we have chosen this as the starting SBRT dose level for the bone metastases.

Patients with asymptomatic low volume locoregional recurrent disease will be allowed to enroll on this study after discussion with the PI. In the case where the low volume recurrence is amenable to SBRT, it will be included in the SBRT treatment. In the case where the low volume recurrence is not amenable to SBRT based on reirradiation risk, then we will follow these lesions with re-imaging scans and reassess at later time points for further local control, which will be allowed on study. Additionally, if these patients fail only at the untreated site (due to the untreated recurrence/disease not being amenable to SBRT) they will be censored in the primary efficacy analysis at that time. Patients with high risk disease in which salvage radiation to the prostate bed is recommended in the absence of lesions noted on scans will be allowed to enroll after discussion with the PI. In these cases, salvage radiation to the prostate bed may occur at the same time as the SBRT.

Radium Ra 223 dichloride will be administered during ADT therapy based on the knowledge of general synergy between ADT and radiation therapies in the treatment of prostate cancer. Radium Ra 223 dichloride has been developed as a treatment given concurrently with ADT therefore safety of that combination has been established. The purpose of radium Ra 223 dichloride therapy is to enhance anticancer effect against known oligo bone metastases required for eligibility for this study, but also treatment of likely invisible bone micrometastases. Laboratory tests will be monitored every 4 weeks and general guidelines for administration of Radium 223 will be followed. These include: for the 1st dose of Radium 223 baseline laboratory test need to be: Hgb ≥ 9.0 g/dL, ANC ≥ 1,500 cells/mm^3, platelets ≥ 100,000 cells/ mm^3. For subsequent infusions (2-6) there is no Hgb requirement, ANC ≥ 1,000 cells/ mm^3, platelets ≥ 50,000 cells/ mm^3.

Up to 7 cycles of protocol therapy are planned in the absence of unacceptable toxicity or disease progression, whichever comes first. If one agent is discontinued due to toxicity, then the participant may continue to receive the other protocol therapy agent(s).

In addition to capturing efficacy endpoints, participants will undergo follow-up up to 5 years to capture long term toxicities (e.g. secondary malignancies) due SBRT and/or radium Ra 223 dichloride.

Efficacy

Prostate-specific antigen (PSA) assessments will occur every cycle during protocol therapy and then every 3 months during Response Follow-up to mimic the ongoing STOM trial [24]. Tumor evaluation will occur pre-SBRT and then at the post Ra-223 visit (post-6 doses of radium Ra 223 dichloride), and during Response Follow-up (every 6 months and at PSA progression).

This study will assess response via PSA levels alone and also use combined PSA and tumor evaluations per the modified Prostate Cancer Working Group 2 criteria [43]. Time to treatment failure will be a primary efficacy endpoint.

Correlative Tumor Studies

Genomic alterations in prostate cancer are being extensively studied although majority of data pertains to metastatic castration resistant prostate cancers (mCRPC) and primary tumors, with relative scarcity of information regarding metastatic hormone sensitive sites. Approximately 90% of mCRPC patients harbor

clinically actionable molecular alterations. Alterations in androgen receptor (AR) signaling pathways, ETS genes, TP53, and PTEN are reported in about 40-60% of patients. Other genomic alterations include*PIK3CA/B*, *RSPO*, *RAF*, *APC*, β-catenin, and *ZBTB16.* Germline and somatic alterations in DNA repair genes gathered significant attention because of potential implications for sensitivity to PARP inhibitors and platin chemotherapy. 23% of mCRPC patients harbor DNA repair pathway aberrations (BRCA2, BRCA1, ATM) and 8% harbor germline findings [44]. Exploratory biomarker analysis on baseline pre-SBRT archival and fresh tissue will be performed. A prostate cancer biomarker panel (e.g. Foundation One platform) will be utilized to analyze genomic alterations in metastatic prostate cancer prior to development of castration resistance.

Correlative Blood Studies

The purpose of the blood correlatives of the study is to assess *in-vivo* effects of radiation on expression of proteins related immune suppression in patients with metastatic prostate cancer. Circulating immune cell populations and plasma levels of cytokines, chemokines and growth factors will be assessed. From this data, we will be able to determine the feasibility of conducting future first-in-human studies involving pathway-specific and novel immunotherapeutic agents for this disease site.

Alkaline Phosphatase Normalization Studies

Alkaline phosphatase levels will be monitored during the study. Increased serum alkaline phosphatase is associated with progression of bone metastases and may predict disease progression and death [21]. The protocol regimen may suppress bone metastases and lead to normalization of alkaline phosphatase levels at the end of protocol therapy in participants with elevated levels of alkaline phosphatase at baseline.

3.0 ELIGIBILITY CRITERIA

Patient MRN	Patient Initials (F, M, L):

Participants must meet all of the following criteria on screening examination to be eligible to participate in the study:

3.1 Inclusion Criteria

Informed Consent and Willingness to Participate

__1. Documented informed consent of participant and/or Legally Authorized Representative.

__2. Agreement to provide archival primary or metastatic tumor tissue if available

Age Criteria, Performance Status, and Life Expectancy

__3. Age: ≥ 18 years

__4. ECOG ≤ 2 (Appendix A)

__5. Life expectancy > 12 months

Nature of Illness and Treatment History

__6. Histologic diagnosis of prostate adenocarcinoma.
Pure small cell carcinoma will be excluded, however component of neuroendocrine /small cell differentiation will be allowed provided that adenocarcinoma constitutes majority of the tissue specimen.

__7. Stage M1. See Appendix B.

Metastatic disease can be documented by bone scan or computed tomography (CT) scan or MRI or PET/CT or the combination of these tests.

__8. Up to 5 metastatic lesions:

Must have at least 1 bone lesion, **AND** each non-visceral lesion should be less than 5 cm

Visceral lesions will be limited to one lung lesion (< 2cm) or one lymph node; no liver lesions allowed. Lymph nodes allowed provided they are not in a field of prior radiation, and if amenable to SBRT (to be reviewed by PI). (note: locoregional recurrence is not considered a “visceral metastatic lesion”. This is discussed more below in #11)

__9. Two lesions can be in close proximity (i.e. within 5cm of each other) if they meet radiation SBRT normal tissue toxicity requirements.

__10. *If have untreated primary prostate cancer*: Must undergo debulking prostatectomy at discretion of treating urologist or definitive radiation therapy. Definitive radiation fields to include close proximity lymph nodes at discretion of treating radiation oncologist. Definitive radiation dose at discretion of treating radiation oncologist (see #14 below: for patients presenting with untreated prostate primary along with oligomets, ADT may begin concurrently with the definitive radiation, for a total of approximately 36 weeks duration)

Patient MRN	Patient Initials (F, M, L):

__11. If had prior treatment to the prostate primary (definitive radiation therapy or prostatectomy, and can include salvage radiation to the prostate bed +/- lymph nodes), no evidence of locally persistent or recurrent prostate cancer on digital rectal exam (DRE) OR imaging studies (CT or MRI).

- Note: patients with asymptomatic low volume locoregional recurrent disease will be allowed to enroll on this study after discussion with the PI. In the case where the low volume recurrence is amenable to SBRT, it will be included in the SBRT treatment. In the case where the low volume recurrence is not amenable to SBRT based on reirradiation risk, then we will follow these lesions with re-imaging scans and reassess at later time points for further local control. Additionally, if these patients fail only at the untreated site (due to the untreated recurrence/disease not being amenable to SBRT) they will be censored in the primary efficacy analysis at that time.

__12. Does not have castration resistant disease

- Castration resistance defined as progression of disease despite serum testosterone level of <50 ng/dL

__13. PSA≥0.2 prior to start of androgen deprivation treatment

PSA value:	Date:

__14. Patients will be receiving approximately 36 weeks of ADT as part of this trial. The 36 weeks of ADT may start prior to consenting to this study. The patient may join the study at any point of the 36-week period of ADT treatment.

- Only Luteinizing hormone-releasing hormone (LHRH) agonist/antagonist treatment is considered ADT; bicalutamide or other antiandrogens used alone do not count.

Patient MRN	Patient Initials (F, M, L):

__15. Patients must be willing to receive bisphosphonate or RANKL inhibitor bone health agents at the dose and schedule consistent with the treatment of bone metastases or prevention of osteoporosis, starting approximately from when the patient begins protocol therapy, until the patient's testosterone reaches normal levels or at the discretion of the PI. Patients who are already on a bone health agent separate from the protocol may continue on this treatment regimen and will not be required to start treatment with an additional bone health agent.

__16. Patients may have received prior hormone therapy at the discretion of the PI. Patients may have received prior targeted therapy in the context of definitive therapy.

__17. Patients may have had one prior systemic non-chemotherapeutic treatment (i.e. immunotherapy, receptor tyrosine kinase inhibitor, antiangiogenic agent, differentiating agent) for recurrent or metastatic disease.

__18. Must have refused standard of care treatment for metastatic disease

__19. Recovered from all acute side-effects (except alopecia) related to previous systemic therapy

Clinical Laboratory Criteria (To be performed within 14 days prior to Day 1 of protocol therapy)

__20. ANC ≥ 1,500/mm^3 **NOTE:** Growth factor support is not permitted to normalize baseline ANC parameters, however subsequent growth factor administration is permitted as standard supportive care.	ANC:	Date:
__21. Platelets ≥ 100,000/mm^3 **NOTE:** Transfusion of blood products are not allowed to normalize baseline blood parameters, however subsequent transfusions are allowed per standard supportive care guidelines.	Plts:	Date:
__22. Hemoglobin (HgB) ≥9.0 g/dL **NOTE:** Transfusion of blood products are not allowed to normalize baseline blood parameters, however subsequent transfusions are allowed per standard supportive care guidelines	HgB:	Date:
__23. Total serum bilirubin ≤ 2 x ULN	ULN: Bil:	Date:
__24. AST ≤ 2.5 x ULN	ULN: AST:	Date:
__25. ALT ≤ 2.5 x ULN	ULN: ALT:	Date:
__26. Creatinine ≤2.5 mg/dL	Serum Cr:	Date:

3.2 Exclusion Criteria

Prior and/or concomitant therapies

__1. Prior Radium Ra 223 dichloride

__2. Prior or concomitant chemotherapy for metastatic or recurrent disease with the following **exceptions**:

- Prior chemotherapy for local primary disease is permitted.

__3. Prior radiation to prior metastatic sites is allowed provided that it is controlled and the total number of metastatic lesions does not exceed 5.

__4. Concomitant radiation treatment to primary prostate site

Patient MRN	Patient Initials (F, M, L):

__5. Bilateral orchiectomy. If unilateral orchiectomy, eligible if testosterone >50 ng/ml.

Other illnesses or conditions

__6. Unstable medical comorbidities (i.e. uncontrolled cardiac comorbidities)

__7. Metastases that in the judgment of investigator-radiologist are not amenable to SBRT

__8. History of brain metastases or who currently have treated or untreated brain metastases

__9. Uncontrolled HIV infection

__10. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns with clinical study procedures.

Noncompliance

__11. Prospective participants who, in the opinion of the investigator, may not be able to comply with all study procedures (including compliance issues related to feasibility/logistics).

Eligibility Confirmed* by (Choose as applicable):	**Print Name**	**Signature**	**Date**
☐ Site PI			
☐ Authorized study MD			
☐ Study Nurse			
☐ Study CRA/ CRC			
☐ Other:_____			
*Eligibility should be confirmed per institutional policies.			

4.0 PARTICIPANT ENROLLMENT

4.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Studies or procedures that were for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained. The informed consent process is to be fully documented (see Section 17.4), and the prospective participant must receive a copy of the signed informed consent document. All screening procedures and their respective windows are detailed in Section 11.0, Study Activity Calendar.

4.2 Participant Enrollment

4.2.1 COH DCC Availability and Contact Information

Eligible subjects will be registered on the study centrally by the Data Coordinating Center (DCC) at City of Hope.

DCC staff are available between the hours of 8.00 am and 5.00 pm PST, Monday through Friday (except holidays). DCC contact information is as follows:

- Phone: (626) 256-4673 ext. 83968
- E-mail: DCC@coh.org

4.2.2 Slot verification and reservation

Designated study staff should call the DCC to verify current dose level (See Table 5.2), slot availability, and to reserve a slot for a specific prospective subject. Slots can only be held for a limited time.

Eligible subjects must be registered **prior** to start of protocol therapy. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a subject does not receive protocol therapy following registration, the subject's registration on the study may be canceled after discussion with the PI. The Data Coordinating Center should be notified of cancellations as soon as possible.

4.2.3 Registration Process

To register a participant the subsequent procedure is to be followed:

1. The study team should contact the DCC via telephone or email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The protocol nurse or CRC will email a copy of the following documents to the DCC:
    - Completed eligibility checklist (printed from Section 3.0 of the protocol)
    - Signed Informed Consent
    - Signed subject's bill of Rights
    - Signed HIPAA authorization form and
    - Provide copies of source documentation only if not readily available as a finalized record in the COH Electronic Medical Record (EMR).
3. After having received all transferred documentation, the DCC will complete the review the documents to verify eligibility, working with the study team as needed to resolve any missing required source elements. A participant failing to meet all protocol eligibility requirements will not be registered.
4. Once eligibility has been confirmed, DCC staff will register the participant by: assigning a subject accession number, register the subject on study centrally into a COH clinical trials management system (e.g. MIDAS), and enter the subject into the eCRF system, Medidata RAVE.
5. Once registration has been completed, DCC staff will send a Confirmation of Registration Form within 24 hours, including the participant study number and cohort assignment (dose level or expansion cohort) to:
    - The site study team: Principal Investigator, treating physician, protocol statistician, protocol nurse, CRC and COH IDS Pharmacy.
    - the COH sponsor team designees

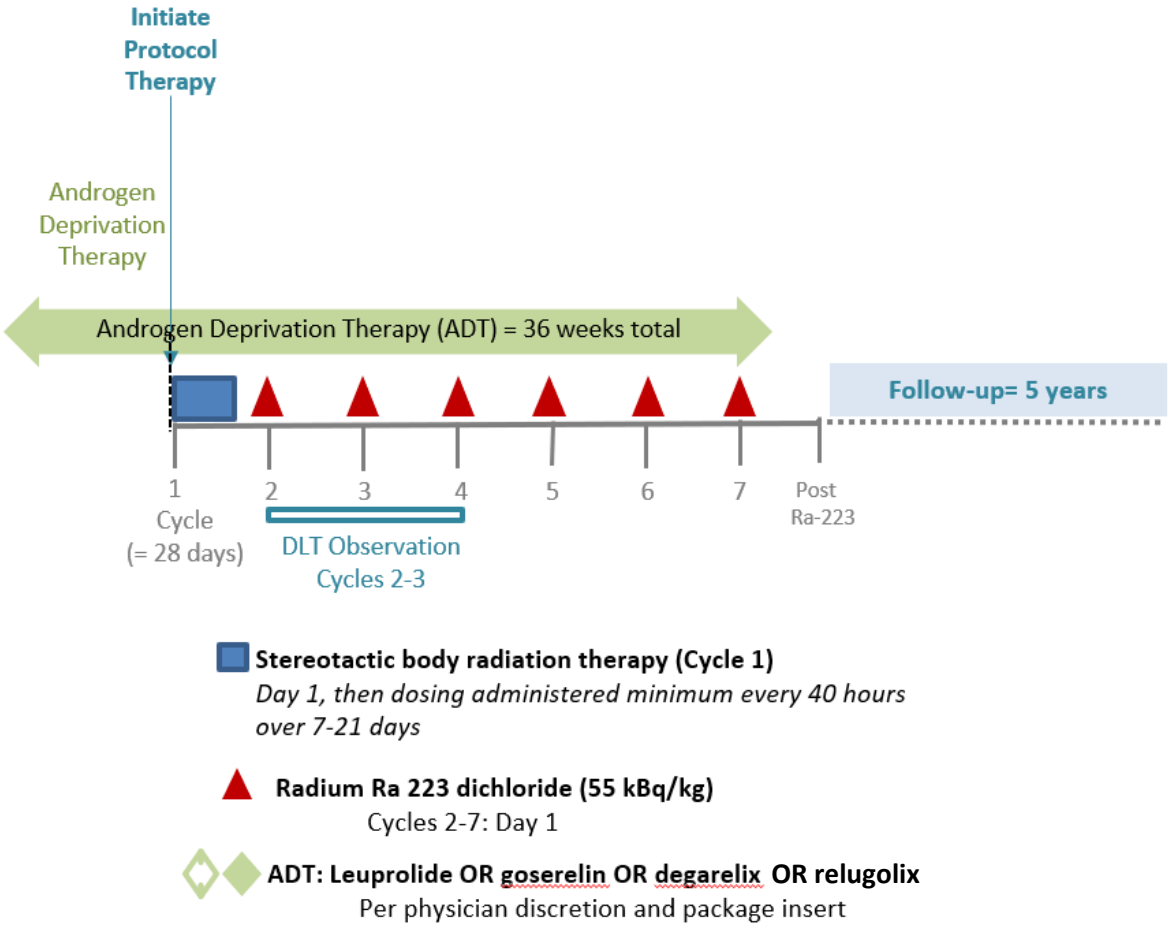
4.3 Screen Failures and Registered Participants Who Do Not begin Study Treatment

The DCC is to be notified of all participants who sign consent but do not meet eligibility criteria or do not initiate protocol therapy.

5.0 TREATMENT PROGRAM

5.1 Treatment Program Overview

This is a single-center open-label, Phase 2 clinical trial of radium Ra 223 dichloride in combination with standard of care androgen deprivation therapy (ADT) and stereotactic body radiation therapy (SBRT) for participants with metastatic castration sensitive prostate cancer (Section 5.3).



Treatment will be administered in an outpatient basis.

SBRT and radium Ra 223 dichloride will be administered in 28 day treatment cycles (Section 5.2). Up to 7 cycles of protocol therapy is planned in the absence of unacceptable toxicity or disease progression, whichever comes first. If one agent is discontinued due to toxicity, then the participant may continue to receive the other protocol therapy agent(s).

While the participant is on protocol therapy, they will receive bisphosphonate or RANKL inhibitor bone health agents at the dose and schedule consistent with the treatment of bone metastases or prevention of osteoporosis, until their testosterone levels are within the normal range (>50 ng/dL) or at the discretion of the PI.

Participants who end protocol therapy will undergo follow-up (Section 5.9). Windows for all assessments and treatments are detailed in Section 11.0.

5.2 Cycle Definition

In the absence of delay due to toxicity, each treatment cycle lasts 28 days.

Cycle 1 Day 1 is defined by the administration of SBRT.

Cycles 2-7 Day 1 is defined by the administration of radium Ra 223 dichloride.

Post Ra-223 is defined as approximately 28 days post-last dose of radium Ra 223 dichloride.

5.3 Treatment Plan

The treatment plan is as follows (Table 5.3). Participants must already have received at least 28 days of ADT (leuprolide OR goserelin OR degarelix OR relugolix) **prior** to initiating Cycle 1 Day 1 SBRT. While on protocol therapy, participants must also receive bisphosphonate or RANKL inhibitor bone health agents at the dose and schedule consistent with the treatment of bone metastases or prevention of osteoporosis, until their testosterone levels reach the normal range or at the discretion of the PI.

Stopping rules may be implemented if there is unacceptable toxicity. For further details see Section 13.0

Table 5.3 Treatment Regimen and Schedule

Agent/Therapy and Route of Administration	Dose	Timing of administration and planned duration
Stereotactic Body Radiation Therapy (SBRT) via *External Beam Radiation via TrueBeam Stx*	9Gy x 3 fractions (bone) 5Gy x 5 fractions (lymph node) 10Gyx5 (lung)	**Cycle 1** Day 1, then dosing administered minimum every 40 hours over 7 to 21 days during Cycle 1
Radium Ra 223 dichloride via *Slow IV over 1 minute*	55 kBq/kg	**Cycles 2-7** Day 1 of each 28-day cycle
Leuprolide **OR** goserelin **OR** degarelix **OR** relugolix *Per package insert/ investigator discretion*		Starting at least 4 weeks prior to SBRT and continuing for a total of 36 weeks as part of regimen on protocol

5.4 Agent Administration

5.4.1 Androgen deprivation therapy

Luteinizing hormone-releasing hormone (LHRH) agonists consisting of either leuprolide OR goserelin OR LHRH antagonist degarelix OR relugolix will be administered per package insert and investigator discretion.

Participants will receive in total 36 weeks of therapy with a LHRH agonist/antagonist; starting at least 28 days prior to initiating Cycle 1 Day 1 stereotactic body radiation therapy.

There is no requirement that the same LHRH agonist/antagonist (whether leuprolide or goserelin or degarelix or relugolix) be administered for the duration of the study.

Dose delay guidelines are described in Section 6.3.

5.4.2 Stereotactic body radiation therapy (SBRT)

Participants **must meet criteria** in Section 6.1 to initiate SBRT on Cycle 1 Day 1.

SBRT will be administered by a trained radiation oncologist. Radiation therapy will initiate at least 28 days following initiation of leuprolide OR goserelin OR degarelix OR relugolix. Participant dosing is described in Table 5.3.

Participants will receive 3 or 5 fractions as determined by the location of the metastases to be irradiated during Cycle 1. There should be a minimum of 40 hours between treatments for an individual metastasis.

For supportive care guidelines refer to Section 5.9.

For administration details refer to Section 9.3. For dose modification refer to Section 6.3.

5.4.3 Radium Ra 223 dichloride

Participants will receive 6 cycles of Radium Ra 223 dichloride following completion of SBRT.

Participants **must meet criteria** in Section 6.2 to receive the **first dose** of radium Ra 223 dichloride.

Radium Ra 223 dichloride will be administered as a slow bolus intravenous injection over 1 minute by a trained physician.

The volume of radium Ra 223 dichloride to be administered to a given participant should be calculated using the:

- Participant's body weight (kg)- calculated **within 30 days** of the dosing day
- Dosage level 55kBq/kg body weight
- Radioactivity concentration of the product (1,100 kBq/mL; 30 microcurie/mL) at reference date
- Decay correction factor to correct for physical decay of Radium Ra 223 dichloride
  - Radium-223 is an alpha particle emitter with a physical t½ of 11.4 days.

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight in kg} \times 55\ \text{kBq/kg body weight}}{\text{Decay factor} \times 1{,}100\ \text{kBq/mL}}$$

Before administration of radium Ra 223 dichloride, the participant must be well hydrated; the participant should be instructed to drink ad libitum.

For additional information regarding administration and preparation refer to Section 9.1.

Prophylactic treatment for nausea and vomiting is not recommended. For supportive care guidelines refer to Section 5.9.

For dose delays due to treatment-related toxicity refer to Section 6.2.

5.5 Assessments and Special Monitoring

For a detailed list of all study procedures including timing and windows, see Section 11.0.

Note: Protocol therapy should be administered on Day 1 of each cycle after all procedures/safety assessments have been completed.

It may be necessary to perform study procedures at unscheduled time points if deemed clinically necessary by the investigator.

5.5.1 Special Monitoring

Gastrointestinal AEs

- Radium Ra 223 dichloride increases AEs such as diarrhea, nausea, and vomiting, which may result in dehydration. Constipation has also been reported in participants receiving radium Ra 223 dichloride.
- Participants should be educated to report signs of dehydration, hypovolemia, urinary retention or renal insufficiency/failure.

Secondary Malignant Neoplasms

- Treatment with radium-223 dichloride contributes to a patient's overall long-term cumulative radiation exposure.
- Long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects.
- Monitor for incidence of osteosarcoma or other secondary neoplasms.

5.6 Criteria for Removal from Protocol Therapy

Participants will receive protocol therapy until one of the following criteria are met:

- Disease progression despite castration levels of testosterone < 50 ng/dL
- Completion of 7 cycles of protocol therapy
- Participant is deemed intolerant to protocol therapy because of toxicity, despite dose modification/ delay
  - **Note:** Participants may continue to receive ADT as clinically indicated and per investigator discretion if the other study agents are discontinued.
- Withdrawal of consent for future protocol therapy (See Section 17.5)
- General or specific changes in the participant's condition that render the participant unacceptable for further treatment in the opinion of the treating investigator.

Once participants meet criteria for removal from protocol therapy, the participant should then proceed to End of Treatment assessments.

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the Electronic Health Record (EHR) and appropriate eCRF.

5.7 Follow-Up

After End of Treatment assessments, all participants will enter follow-up for a maximum of 5 years. This is comprised of:

- **Response Follow-up**- for those who have yet progress
- **Long-term Follow-up**- for all participants who have progressed OR completed Response Follow-Up for survival and long-term toxicities. This follow-up will be performed typically via medical record review.

Assessment time points and windows are detailed in Section 11.0.

5.8 Duration of Study Participation

The reason(s) for discontinuing study participation should be documented and may include:

- Completion of study activities (treatment and follow-up)
- Withdrawal of consent (See Section 17.5)
- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- At the discretion of the investigator for safety, behavioral, study termination or administrative reasons

The reason for study completion and associated date must be documented in the source documentation and the study-specific case report form (CRF). The participant's status is to be modified in the COH CTMS once the participant completes the study.

5.9 Supportive Care, Prohibited Medications and Concomitant Therapy

If concomitant therapy must be added or changed, including over-the-counter medications or alternative therapies, the reason and name of the agent/therapy should be reported in the eCRF and recorded in the EHR.

5.9.1 Prohibited Therapy

The following therapies are prohibited from **Cycle 1 Day 1 until completion of End of Treatment visit procedures**.

- Other investigational therapy/agent
- Other anticancer agents
- Antiandrogen agents (bicalutamide, flutamide)
- EXCEPTION: patients that enrolled on the study with asymptomatic low volume locoregional recurrent disease which was not amenable to SBRT at the time of enrollment will be followed with re-imaging scans. They will be reassessed at later time points during the study for further local control if needed.

5.9.2 Supportive Care

With the exception of prohibited therapies (see Section 5.9.1), participants should receive prophylactic or supportive care as clinically indicated per institutional policies.

Treatment /prevention of osteoporosis

- Treatment with bisphosphonates or RANK Ligand inhibitors (e.g. denosumab) is required
- Calcium supplementation, Vitamin D are also highly encouraged.
- For the treatment /prevention of osteoporosis doses and schedule must be consistent with the treatment or prevention of osteoporosis.

Non-pathological fractures

- If in weight-bearing bones follow dose delay guidelines in Section 6.3.

Pathological fractures

- Pathological fractures may occur as the result of either progressive disease or increased physical activity associated with significant pain palliation.
- Treat in a manner that attempts to maintain the best functional status and quality of life.

Erythropoietin-stimulating factors, granulocyte colony stimulating factors

- Allowed

Prophylactic treatment for gastrointestinal AEs

- Prophylactic treatment for nausea and vomiting not recommended; however, anti-emetic drugs may be used when needed.
  - Laxative can be continued as concomitant medication, but start of prophylactic treatments before radium Ra 223 dichloride injection is not recommended. Laxative may be used when needed.
- No prophylactic treatment for diarrhea is recommended.

Surgery

- 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.

6.0 CRITERIA FOR INITIATINGSBRT AND RADIUM RA 223 DICHLORIDE & DOSE DELAY GUIDELINES

6.1 Criteria to START SBRT (Cycle 1 Day 1)

Table 6.1 details criteria participants must meet to initiate SBRT.

Table 6.1 Cycle 1 Day 1 SBRT Administration Criteria

Criteria to be met in order to START SBRT	Action if criterion to the RIGHT is NOT met
1. ANC ≥ 1,500/mm^3 **NOTE:**Growth factor supportis not permitted to normalize baseline ANC parameters, however subsequent growth factor administration is permitted as standard supportive care.	Permanently discontinue protocol therapy if unable to initiate SBRT 28 (+ 7) days post-1st dose of ADT (time constraint exception is in patients who started ADT concurrent with radiation tx or surgery). ADT may continue as a non-protocol therapy if clinically indicated.
2. Platelets ≥ 100,000/mm^3 *	
3. Hgb ≥ 9.0 g/dL*	
***NOTE:**Transfusion of blood products are not allowed to normalize baseline blood parameters, however subsequent transfusions are allowed per standard supportive care guidelines.	
4. Not experienced ≥ **recurrent** Grade 3 ADT-related AE	Permanently discontinue protocol therapy.
5. ADT related AEs ≤ Grade 2	Permanently discontinue protocol therapy if unable to initiate SBRT 28 (+7) days post-1st dose of ADT (time constraint exception is in patients who started ADT concurrent with radiation tx or surgery). ADT may continue as non-protocol therapy if clinically indicated.
6. Absence of toxicity not present at baseline that might adversely affect participation or results in a reasonable delay prior to initiating SBRT	Permanently discontinue protocol therapy. ADT may continue as non-protocol therapy if clinically indicated.

6.2 Criteria to START Radium Ra 223 Dichloride (Cycle 2 Day 1)

Table 6.2 details criteria participants must meet to initiate radium Ra 223 dichloride therapy.

Table 6.2 Cycle 2 Day 1 Radium Ra 223 Dichloride START Criteria

Criteria to be met in order to START 1st dose of radium Ra 223 dichloride	Action if criterion to the RIGHT is NOT met
1. ANC ≥ 1,500/mm^3 **NOTE:**Growth factor supportis not permitted to normalize baseline ANC parameters, however subsequent growth factor administration is permitted as standard supportive care.	Delay initiating radium Ra 223 dichloride until criterion is met. Permanently discontinue radium Ra 223 dichloride if unable to initiate within 28 days of planned dose.
2. Platelets ≥ 100,000/mm^3 *	
3. Hgb ≥ 9.0 g/dL*	
* **NOTE:**Transfusion of blood products are not allowed to normalize baseline blood parameters, however subsequent transfusions are allowed per standard supportive care guidelines	
4. Not experienced ≥ **recurrent** Grade 3 treatment-related AE	Permanently discontinue protocol therapy.
5. Treatment related AEs ≤ Grade 2	Delay initiating radium Ra 223 dichlorideuntil resolution of treatment-related AE to ≤ Grade 2. Permanently discontinue radium Ra 223 dichloride if unable to initiate within 28 days of planned dose.
6. Absence of unrelated toxicity not present at baseline that might adversely affect participation or results in a reasonable delay prior to initiating radium Ra 223 dichloride	Permanently discontinue radium Ra 223 dichloride **OR** Delay initiating until criterion is met; permanenetly discontinue radium Ra 223 dichloride if unable to initiate within 28 days of planned dose.

6.3 Dose Delay Guidelines

- Toxicities will be graded using the NCI CTCAE v 5.0.
- Baseline values are from the last values obtained prior to treatment.
- If one agent is permanently discontinued, then the participant may continue with the other agent(s).
- **SBRT**
  - If there is concern of toxicity to critical normal structures the SBRT dose will be sculpted according to national guidelines to conform to limit risk of toxicities to normal structures to ≤ 5%.
  - If a participant does not complete the SBRT segment as planned, then that participant may receive the other study agent(s)as clinically indicated.
- **Radium Ra 223 dichloride and ADT**
  - Only dose delays are permitted
  - See Table 6.3 for dose delay guidelines
  - Participants may continue to receive ADT as clinically indicated and per investigator discretion if radium Ra 223 dichloride is discontinued.

Table 6.3 Dose Delay Guidelines

Toxicity	Agent most likely attributed to toxicity	Treatment Delay Guidelines
Hematologic		
Neutropenia (ANC) Grade 3/4 G3: 500- <1000/mm^3 G4: *<500/mm^3*	*Radium Ra 223 Dichloride*	*First occurrence* • Hold the planned dose • Resume when toxicity resolves to ≤ Grade 2 **AND**> 14 days have passed from growth factor support discontinuation • Permanently discontinue study agent if the planned dose is delayed > 28 days. *Second occurrence* • Permanently discontinue study agent.
Febrile neutropeniaGrade 3/4 *G3: ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.* *G4: Life-threateningconsequences; urgentintervention indicated*	*Radium Ra 223 Dichloride*	*First occurrence* • Hold the planned dose • Resume when ANC resolves to ≤ Grade 2 **AND**> 14 days have passed from growth factor support discontinuation • Permanently discontinue study agent if the planned dose is delayed > 28 days. *Second occurrence* • Permanently discontinue study agent.

Toxicity	Agent most likely attributed to toxicity	Treatment Delay Guidelines
Thrombocytopenia Grade 3/4 *G3: 25,000-<50,000/mm^3* *G4: <25,000/mm^3*	*Radium Ra 223 Dichloride*	*First occurrence* • Hold the planned dose • Resume when toxicity resolves to ≤ Grade 2 **AND**> 14 days have passed from last platelet transfusion • Permanently discontinue study agent if the planned dose is delayed >28 days. *Second occurrence* • Permanently discontinue study agent.
Other Non-hematological toxicities		
≥ Grade 3	*Leuprolide* *Goserelin* *Degarelix* *Relugolix*	*First occurrence* • Hold next planned dose until toxicity resolves to ≤ Grade 2. • Permanently discontinue ADT if the planned dose is delayed > 42 days. – **Exception:** if testosterone level remains in the castrated state (<50 ng/dL), then participantcan remain on the study following consultation with the Study PI or designee. *Second occurrence* • Permanently discontinue protocol therapy.
≥ Grade 3	*Radium Ra 223 Dichloride*	*First occurrence* • Hold next planned dose until toxicity resolves to ≤ Grade 2. • Permanently discontinue study agent if the planned dose is delayed > 28 days. *Second occurrence* • Permanently discontinue protocol therapy.
Non-hematological toxicities- UNRELATED		
Any Grade	*UNRELATED*	• Maintain treatment with study agent/ regimen. • Interruption of protocol therapy is permitted if the investigator consults with the Study PI to determine that this is in the best interest of the participant.

7.0 ADVERSE EVENTS LIST

7.1 Leuprolide

The expected toxicities for leuprolide are as follows (*signifies ≥ 20%; no asterisk signifies 3-20%, and † signifies <3%):

Cardiac	Trachycardia, bradycardia, angina, palpitation, arrthythmia†, atrial fibrillation†, congestive heart failure†, syncope†
Gastrointestinal	Nausea*, vomiting*, altered bowel function, ulcer, intestinal obstruction, constipation, diarrhea, gastroenteritis/colitis, gastrointestinal hemonrrage†
General Disorders and Administration Site	Edema
Immune system	Flu-like syndrome, allergic reaction†
Infections and infestations	Infection
Investigations (excluding hematological labs)	BUN increase, creatinine increase, bicarbonate decrease, hyperphosphatemia, hyperuricemia, hypoalbuminemia, hypoproteinemia
Metabolism and Nutrition	Dehydration, hyperlipidemia, weight gain/loss
Musculoskeletal and Connective Tissue	Weakness, bone pain, joint disorder, myalgia, paresthesia
Nervous system	Headache*, pain*, insomnia*,nervousness, anxiety, confusion, fatigue, dizziness/vertigo, seizure†
Psychiatric	Depression*
Renal and urinary	Urinary disorders, bladder spasm, urinary retention
Respiratory, Thoracic and Mediastinal	Emphysema, epistaxis, pleural effusion, pulmonary edema, dyspnea, cough
Skin and Subcutaneous Tissue	Skin reaction, ache, alopecia, brusing, pruritus, rash
Vascular	Hyper/hypotension, deep thombophlebitis

7.2 Goserelin

The expected toxicities for goserelin are as follows (* signifies ≥ 20%; no asterisk signifies 3-20%, and † signifies <3%):

Blood and lymphatic (including hematological labs)	Anemia
Cardiac	Congestive heart failure, palpitation, trachycardia, cerebrovascular accident†, myocardial infarction†
Eye	Amblyopia, dry eyes
Gastrointestinal	Anorexia, appetite increase, nausea, abdominal pain, constipation, diarrhea, dyspepsia, flatualence, ulcer, vomiting, xerostomia
General Disorders and Administration Site	Sweating*, tumor flare*, injection site reaction, volice alteration, fever

Infections and infestations	Infection, flu syndrome
Investigations (excluding hematological labs)	Weight gain/loss
Metabolism and Nutrition	Hyperglycemia
Musculoskeletal and Connective Tissue	Bone mineral density decrease*, weakness, arthralgia, back pain, hypertonia, bone/joint pain, leg cramps, myalgia, paresthesia
Nervous system	Headache*, dizziness, pain
Psychiatric	Anxiety, depression, insomnia, emotional lability
Renal and urinary	Urinary tract infection, urinary obstruction, urinary frequency
Vascular	Hypertension, vasodilation

7.3 Degarelix

The expected toxicities for degarelix are as follows (* signifies ≥ 20%; no asterisk signifies 3-20%, and † signifies <3%):

Cardiac	Hot flashes*
Endocrine	Gynecomastia†, testicular atrophy†
Gastrointestinal	Diarrhea†, nausea†, constipation
General Disorders and Administration Site	Injection site pain/erythema*, injection site swelling/induration/nodule, fatigue, chills, fever†, night sweats†, hyperhidrosis†
Infections and infestations	Urinary tract infection
Investigations (excluding hematological labs)	Elevation in transaminases/GGT
Metabolism and Nutrition	Weight gain
Musculoskeletal and Connective Tissue	Back pain, arthralgia
Nervous system	Asthenia†, dizziness†, headache†, insomnia†
Urologic	Erectile dysfunction†
Vascular	Hypertension

7.4 Relugolix

The expected toxicities for relugolix are as follows (* signifies ≥ 20%; no asterisk signifies 3-20%, and † signifies <3%):

Vascular	Hot flush*, stroke†
Muscoloskeletal and Connective Tissue	Musculoskeletal pain*, fracture†
General	Fatigue*
Gastrointestinal	Diarrhea, constipation, abdominal pain†

Investigations (excluding hematological labs)	Increased glucose*, increased triglycerides*, increased alanine aminotransferase*, increased aspartate aminotransferase, increased transaminases†
Cardiac	Myocardial infarction†, arrhythmia†, atrioventricular block†, cardiac failure†
Blood and lymphatic	Decreased hemoglobin*, hemmorrhage†
Renal	Urinary tract infection†, acute kidney injury†
Respiratory	Pneumonia†

7.5 Stereotactic body radiation therapy

Adverse events related to radiation therapy are depending on location of the tumor (i.e. spine metastases in thoracic spine has more risk to lung than spine metastases in pelvis or lumbar spine. As with any radiation there is a risk of secondary malignancies but usually reported 10+ years after the initial radiation treatment course.

- **Spine Metastases**
  - Radiation Myelitis: paresthesia, sensory changes, motor weakness, permanent motor or sensory injury. Injury can be permanent and lead to loss of neurological function.
  - Compression fracture of treated spine metastases/vertebra
  - Radiation Esophagitis
  - Radiation Laryngitis/Pharyngitis
  - Tracheal Injury
  - Radiation Pneumonitis
- **Bone/osseous metastases**
  - *Common> 10%*:
    - *Skin and Subcutaneous Tissue*: erythema, desquamation, alopecia
  - *Less common 1-10%*:
    - *General Disorders and Administration Site*: pain, edema,
    - *Nervous System*: neuralgia
    - *Injury, poisoning and procedural complications*: fracture
- **Abdominal/pelvic lymph node metastases**
  - Common> 10*:
    - *Blood and lymphatic*: Change in blood counts
    - *General Disorders and Administration Site*: Fatigue
    - *Skin and Subcutaneous Tissue*: skin irritation, redness, itchiness,
  - Less common 1-10%:
    - *Gastrointestinal*: nausea, vomiting, diarrhea
  - Uncommon but serious< 1%:
    - *Hepatic*: liver failure
    - *Gastrointestinal*: bowel perforation requiring emergent surgery

7.6 Radium Ra 223 dichloride

7.6.1 Radiation exposure:

In general, administration of radioactive drugs involves a potential risk for third parties because of radiation from the participant and possible contamination by spilling urine or feces. When radium Ra 223 dichloride has been injected intravenously into a participant, the risk for external radiation exposure to third parties is extremely low, because of the short range of theα particles (<100 µm) and the low portion of β and γ radiation. For these reasons, the product can be administered on an out-patient basis.

To minimize the risk of contamination, participants and his caregivers will receive oral and written instructions regarding hygiene precautions to abide by after receiving radium Ra 223 dichloride.

7.6.2 Side-effects:

The expected toxicities for radium Ra 223 dichloride are as follows (no asterisk signifies ≥ 10%; * signifies 1-10%, and † signifies <1%):

Blood and lymphatic (including hematological labs)	Anemia, lymphocytopenia, leukopenia, thrombocytopenia, neutropenia
Gastrointestinal	Nausea, diarrhea, vomiting
General Disorders and Administration Site	Peripheral edema, injection site reaction*
Metabolism and Nutrition	Dehydration*
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Treatment related secondary malignancy†
Renal and urinary	Renal failure and impairment*

8.0 DATA & SAFETY MONITORING, ADVERSE EVENT AND UNANTICIPATED PROBLEM REPORTING

8.1 COH Data and Safety Monitoring Plan

Definition of Risk Level

This is a Risk Level 3 study as defined in the City of Hope Institutional Data and Safety Monitoring Plan. This determination was made because this study was deemed IND exempt by the FDA.

Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) is responsible for monitoring the data and safety of this study. The PMT consists of the Principal Investigator (PI), Biostatistician, Research Protocol Nurse, and Clinical Research Coordinator.

The PMT is required to submit periodic status reports (i.e., the PMT Report) according to the frequency prescribed in the City of Hope Institutional Data and Safety Monitoring Plan. Important decisions made during PMT meetings (i.e., dose de-escalation, etc.) only need to be noted in the PMT Report submitted to the Data and Safety Monitoring Committee (DSMC).

Adverse Events and Serious Adverse Events

The PI or their designee will be responsible for determining the event name, assessing the severity (i.e., grade), expectedness, and attribution of all adverse events.

Adverse Event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Reporting Non-serious Adverse Events – Adverse events will be collected after the patient is given the study treatment or any study related procedures. Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the PMT Report.

Serious Adverse Event (SAE) [Modified from the definition of unexpected adverse drug experience in 21 CFR 312.32] - defined as *any expected* or *unexpected adverse event*s that result in any of the following outcomes:

- Death
- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Reporting Serious Adverse Events - begins after study treatment or any study related procedures. All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to the approved City of Hope's Institutional policy. Serious Adverse Events that require expedited reporting will be submitted electronically using iRIS.

Adverse Event Name and Severity

The PI will determine the adverse event name and severity (grade) by using the most current CTCAE version 5.0.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event, OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Unexpected Adverse Event [21 CFR 312.32 (a)] – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Adverse Event Attribution

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Definite** - The AE is clearly related to the investigational agent or study procedure and unrelated to any other cause.
- **Probable** - The AE is likely related to the investigational agent or study procedure and unlikely related to other cause(s).
- **Possible** -The AE may be related to the investigational agent or study procedure and may be related to another cause(s).
- **Unlikely** -The AE is doubtfully related to the investigational agent or study procedure and likely related to another cause(s).
- **Unrelated** -The AE is clearly not related to the investigational agent or study procedure and is attributable to another cause(s).

Deviations and Unanticipated Problems

Deviation - A deviation is a divergence from a specific element of a protocol that occurred without prior IRB approval. Investigators may deviate from the protocol to eliminate immediate hazard(s) for the protection, safety, and well-being of the study subjects without prior IRB approval. For any such deviation, the PI will notify the COH DSMC and IRB within 5 calendar days of its occurrence via iRIS in accordance with the Clinical Research Protocol Deviation policy.

Single Subject Exception (SSE)

An SSE is a planned deviation, meaning that it involves circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient. It is a deviation that is anticipated and receives prior approval by the PI and the IRB. The SSE must be submitted as a "Single Subject Exception Amendment Request" via iRIS in accordance with IRB guidelines and the Clinical Research Protocol Deviation policy. An IRB approved SSE does not need to be submitted as a deviation to the DSMC.

Unanticipated Problem (UP) – Any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Any UP that occurs during study conduct will be reported to the DSMC and IRB in accordance with the City of Hope's Institutional policy using iRIS.

8.2 Exceptions to Expedited Reporting

The following AEs **DO NOT** require an expedited report **UNLESS** results in hospitalization (≥ 24 hours). However, they still must be reported through the routine mechanism in the eCRFs.

CTCAE SOC	List of Grade 1-2 Adverse Events
Blood and lymphatic (including hematological labs)	Leukopenia, neutropenia, anemia
Eye	Vision disorder
Gastrointestinal	Nausa, vomiting, diarrhea, constipation, dyspepsia, flatualence,
General Disorders and Administration Site	Fatigue, edema
Metabolism and Nutrition	Decreased appetite
Nervous system	Dizziness, dysgeusia, fatigue, headache
Investigations	Blood testosterone decreased, ALT/AST increase
Skin and Subcutaneous Tissue	Skin reaction, alopecia, bruising, pruritus, rash

8.3 Reporting to Bayer

The PI or designee will forward reports to Bayer in a timely fashion per below stated guidelines.

1. Expedited reports that meet Unanticipated Problem (UP) criteria will be promptly forwarded to Bayer **within 24 hours** of being aware of the event via email: DrugSafety.GPV.US@bayer.com.
2. Aggregate safety information will be reported to Bayer at time of COH DSMC report.

9.0 AGENT INFORMATION

9.1 Radium Ra 223 dichloride

Radium Ra 223 dichloride is indicated for treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

For additional details refer to the Investigator Brochure.

9.1.1 Other Name

Xofigo®

9.1.2 Description

Type of radiotherapeutid agent:	Alpha particle-emitting pharmaceutical
Formula:	^{223}RaCl2
Molecular weight:	293.9 g/mol.

9.1.3 Mechanism of Action

The divalent cation (223Ra2+) radium Ra 223 dichloride mimics calcium and selectively targets bone, specifically areas of bone metastases, by forming complexes with the bone mineral hydroxyapatite. The high linear energy transfer of alpha emitters (80 Kiloelectronvolt/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in a potent and localized anti-tumor effect. The alpha particle range from radium Ra 223 dichloride is less than 100 micrometers (less than 10 cell diameters) which limits damage to the surrounding normal tissue.

9.1.4 Pharmacokinetics

Distribution	15 minutes post injection, ~20% of the injected radioactivity remains in the blood. At 4 hours ~ 4% in the blood, by 24 hours <1% in blood. Observed in the bone 10 minutes post-injection. At 4 hours post-injection ~ 61% in bone and 49% in intestine.
Metabolism:	N/A
Elimination:	~63% of radioactivity excreted within 7 days post-injection. Feces ~13%, urine ~2%
Half-life:	11.4 days

9.1.5 Human Toxicity

See Section 7.4.

9.1.6 Formulation

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

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.

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

The volume per vial is 6 mL, corresponding to 6.6 MBq at the reference day.

9.1.7 Storage

The Radium Ra 223 dichloride vials must be stored inside their lead container in a secure facility.

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

9.1.8 Handling and Dispensing

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

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

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

9.1.9 Radiation Protection

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

9.1.9.1 For drug handling

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

9.1.9.2 For patient care

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

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

9.1.10 Dose Calibration

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

Different clinical study centers possess dose calibrators from various suppliers; thus, the isotope calibration factor may differ from center to center. Consequently, each center must perform the Radium Ra 223 dichloride dial setting on their relevant dose calibrator(s).

9.1.11 Dosimetry

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

For an administered activity of 3.65 MBq (0.0987 mCi) (55kBq, 0.0015mCi) per kg body weight to a 73-kg adult, the calculated absorbed doses to the bone (osteogenic cells) is 4.2050 Gy (420.5 rad) and to the red marrow is 0.5066 Gy (50.66 rad). The calculated absorbed doses to the main excretory organs are 0.0265 Gy (2.65 rad) for the small intestine wall, 0.1180 Gy (11.8 rad) for the upper large intestine wall and 0.1696 Gy (16.96 rad) for the lower large intestine wall.

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

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

9.1.12 Dose Calculation

The patient dose is calculated based on date of injection, a decay correction factor specific to number of days from reference date applied to correct for physical decay of radium-223, and patient weight (calculated within 30days of the dosing day).

A table with decay correction values according to physical decay of the study medication will be provided with every shipment of radium Ra 223 dichloride.

Refer to Section 5.4.3for the dose calculation formula.

9.1.13 Dose Preparation

Personnel should use appropriate protective clothing and equipment during syringe filling and application to prevent contamination with the radioactive solution (medical gloves/protective glasses).

The individual responsible for study drug preparation will draw the correct volume of study drug into a syringe.

The size of the syringe should be chosen according to the applied volume to reach the required dosing accuracy.

Radium Ra 223 dichloride should not be diluted or mixed with any solutions. Do not store above 40°C (104°F).

If the vials have been stored in a refrigerator, they should be left at room temperature for 1 hour prior to use, since cold material should not be injected in a patient. Store radium Ra 223 dichloride in the original container or equivalent radiation shielding. This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

9.1.14 Dose administration

1. Aseptic technique should be used in the administration of radium Ra 223 dichloride.
2. The syringe should be handed over to the individual who will perform the injection.
3. The study medication will be administered as a bolus intravenous (IV) injection (up to 1 minute).
4. After administration, the equipment used in connection with the preparation and administration of drug is to be treated as radioactive waste and should be disposed in accordance with local procedure for the handling of radioactive material.

Refer to Section 5.4.3 for additional administration details.

9.1.15 Supplier

The investigational agent will be supplied free of charge by Bayer.

9.1.16 Ordering

1. The Cardinal Product Request Form should be faxed to Cardinal Health Denver each time a dose is needed. Contact details can be found on the Cardinal Product Request Form.
2. The order form must include the IIR Study number which is **IIR-US-2016-1801**.
3. The patient's weight should be calculated **within 30days** of the dosing day.
4. The patient dose should be requested **at least 3 business days prior** to time of agent administration so that the volume of agent to be disbursed can be calculated.
5. The form must be completed for each and every dose being ordered.
6. Bulk supply will not be provided due to the short half-life of radium Ra 223 dichloride and possible changes inpatient weight.

9.1.17 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational agent using a drug accountability log.

9.1.18 Destruction and Return

The investigator is responsible for keeping accurate records of the clinical supplies received from Bayer or designee, the amount dispensed to participants, and the amount remaining at the conclusion of the trial.

Any unused agent at the end of the study, expired agent, and damaged agent will be destroyed according to applicable federal, state, local and institutional guidelines and procedures.

Destruction will be documented in a drug accountability log.

The certificate of destruction for radium Ra 223 dichloride should be sent to Bayer.

9.2 Androgen Deprivation Therapy

ADT therapy will consist of treatment with either LHRH agonist leuprolide (Section 9.2.1), goserelin (Section 9.2.2) or LHRH antagonist degarelix (Section 9.2.3) or relugolix (Section 9.2.4) per investigator discretion.

9.2.1 Leuprolide

Leuprolide is indicated for:

- Endometriosis
- Advanced prostate cancer
- Breast cancer
- Infertilities
- Paraphilia
- Uterine fibroids

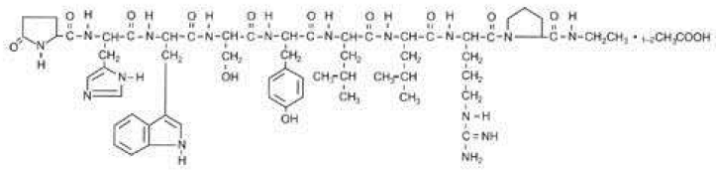
Please refer to the package insert for additional details.

9.2.1.1 Other Names

Lupron Depot®, leuprolide acetate

9.2.1.2 Description

Structural formula:



Empirical formula:	$C_{61}H_{88}N_{16}O_{14}$
Molecular weight:	1269.473 g/mol
Chemical name:	5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-Dleucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate

9.2.1.3 Mechanism of Action

Leuprolide binds to the gonadotropin releasing hormone receptor and acts as a potent inhibitor of gonadotropin secretion.

9.2.1.4 Pharmacokinetics

Elimination half-life:	3 hours
Tmax:	IM: 4 hours, subQ~3-5 hours
Protein binding:	43-49%
Metabolism:	Hydolysis via peptidase enzyme
Excretion:	Renal (< 5% unchanged)

9.2.1.5 Human Toxicity

See Section 7.1 for details.

9.2.1.6 Formulation

Intramuscular or subcutaneous injection; monthly or every 3-months.

9.2.1.7 Storage, Handling, Preparation

Follow package insert instructions.

9.2.1.8 Dose and Administration

See Section 5.4.1for additional administration guidelines. Dosing will be per package insert and investigator discretion.

9.2.1.9 Supplier

Leuprolide is available commercially.

9.2.2 Goserelin

Goserelin is indicated for:

- Locally confined carcinoma of the prostate
- Advanced carcinoma of the prostate
- Breast cancer
- Endometriosis

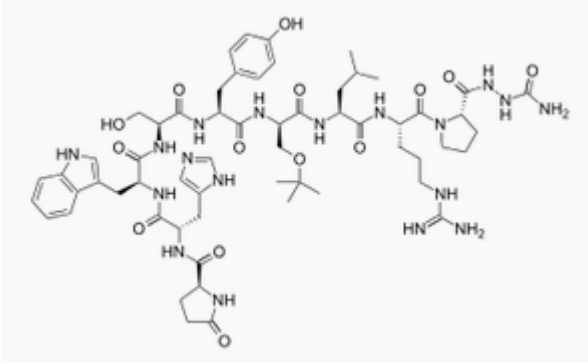
Please refer to the package insert for additional details.

9.2.2.1 Other Names

Zoladex®, goserelin acetate

9.2.2.2 Description

Structural formula:



Empirical formula:	$C_{59}H_{84}N_{18}O_{14}$
Molecular weight:	1269.433 g/mol
Chemical name:	(2S)-1-[(2S)-2-[(2S)-2-[(2R)-3-(tert-butoxy)-2-[(2S)-2-[(2S)-3-hydroxy-2-[(2S)-2-[(2S)-3-(1H-imidazol-5-yl)-2-[(2S)-5-oxopyrrolidin-2-yl]formamido}propanamido]-3-(1H-indol-3-yl)propanamido]propanamido]-3-(4 hydroxyphenyl)propanamido]propanamido]-4-methylpentanamido]-5-[(diaminomethylidene)amino]pentanoyl]-N-(carbamoylamino)pyrrolidine-2-carboxamide

9.2.2.3 Mechanism of Action

Goserelin is a synthetic decapeptide analogue of LHRH. Goserelin acts as a potent inhibitor of pituitary gonadotropin secretion when administered in the biodegradable formulation. The result is sustained suppression of LH and serum testosterone levels.

9.2.2.4 Pharmacokinetics

Elimination half-life:	4.2 hours (male); 2.3 hours (female)
Absorption:	Rapid
Protein binding:	27%
Metabolism:	Liver hydolysis of the C-terminal amino acids
Excretion:	Renal 90%

9.2.2.5 Human Toxicity

See Section 7.2 for details.

9.2.2.6 Formulation

Subcutaneous injection; monthly or every 3-months.

9.2.2.7 Storage, Handling, Preparation

Follow package insert instructions.

9.2.2.8 Dose and Administration

See Section 5.4.1for additional administration guidelines. Dosing will be per package insert and investigator discretion.

9.2.2.9 Supplier

Goserelin is available commercially.

9.2.3 Degarelix

Degarelix is indicated for:

- Advanced carcinoma of the prostate

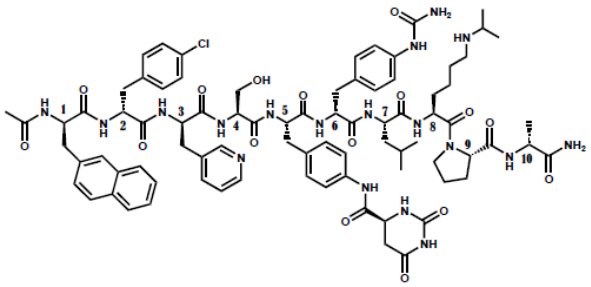
Please refer to the package insert for additional details.

9.2.3.1 Other Names

Firmagon®

9.2.3.2 Description

Structural formula:



Empirical formula:	$C_{82}H_{103}N_{18}O_{16}Cl$
Molecular weight:	1632.3 Da
Chemical name:	(2S)-1-[(2S)-2-[(2S)-2-[(2R)-3-(tert-butoxy)-2-[(2S)-2-[(2S)-3-hydroxy-2-[(2S)-2-[(2S)-3-(1H-imidazol-5-yl)-2-[(2S)-5-oxopyrrolidin-2-yl]formamido}propanamido]-3-(1H-indol-D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-Dphenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-4-[[[(4S)-hexahydro-2,6-dioxo-4pyrimidinyl]carbonyl]amino]-L phenylalanyl-4-[(aminocarbonyl)amino]-D-phenylalanyl-L leucyl-N6–(1methylethyl)-L-lysyl-L-prolyl

9.2.3.3 Mechanism of Action

Degarelix is a GnRH receptor antagonist. It binds reversibly to the pituitary GnRH receptors, thereby reducing the release of gonadotropins and consequently testosterone.

9.2.3.4 Pharmacokinetics

Elimination half-life:	Loading dose (subcut) ~53 days, maintenance dose (subcut) ~31 days
Absorption:	Rapid
Protein binding:	90%
Metabolism:	Peptide hydrolysis during passage of hepato-biliary system
Excretion:	Renal 20-30%, hepatobiliary 70-80%

9.2.3.5 Human Toxicity

See Section 7.2 for details.

9.2.3.6 Formulation

Subcutaneous injection; monthly.

9.2.3.7 Storage, Handling, Preparation

Follow package insert instructions.

9.2.3.8 Dose and Administration

See Section 5.4.1for additional administration guidelines. Dosing will be per package insert and investigator discretion.

9.2.3.9 Supplier

Degarelix is available commercially.

9.2.4 Relugolix

Relugolix is indicated for:

- Advanced carcinoma of the prostate

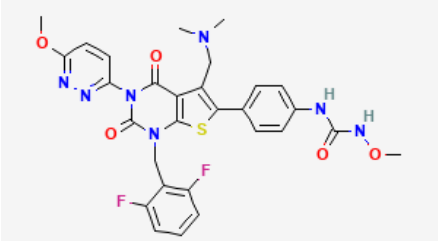
Please refer to the package insert for additional details.

9.2.4.1 Other Names

Orgovyx™, Relumina, RGX, RVT-601, TAK-385

9.2.4.2 Description

Structural formula:



Empirical formula:	$C_{29}H_{27}F_2N_7O_5S$
Molecular weight:	623.6 Da
Chemical name:	1-[4-[1-[(2,6-difluorophenyl)methyl]-5-[(dimethylamino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxothieno[2,3-d]pyrimidin-6-yl]phenyl]-3-methoxyurea

9.2.4.3 Mechanism of Action

Relugolix is a nonpeptide GnRH receptor antagonist that competitively binds to pituitary GnRH receptors, thereby, reducing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and consequently testosterone.

9.2.4.4 Pharmacokinetics

Elimination half-life:	The mean effective half-life of relugolix is 25 hours and the mean (CV%) terminal elimination half-life is 60.8 (11%) hours. The mean (CV%) total clearance of relugolix is 29.4 (15%) L/h and the renal clearance is 8 L/h.
Absorption:	Relugolix is a substrate for intestinal P-gp. The mean (CV%) absolute bioavailability of relugolix is approximately 12% (62%). The median (range) Tmax of relugolix is 2.25 hours (0.5 to 5.0 hours).
Protein binding:	Plasma protein binding of relugolix is 68 to 71%, primarily to albumin and to a lesser extent to α_1-acid glycoprotein. The mean blood-to-plasma ratio is 0.78.
Metabolism:	Relugolix is metabolized primarily by CYP3A and to a lesser extent by CYP2C8 in vitro

Excretion:	After oral administration of a single 80-mg radiolabeled dose of relugolix, approximately 81% of the radioactivity was recovered in feces (4.2% as unchanged) and 4.1% in urine (2.2% as unchanged).

9.2.4.5 Human Toxicity

See Section 7.4 for details.

9.2.4.6 Formulation

Tablets, taken orally once daily

9.2.4.7 Storage, Handling, Preparation

Follow package insert instructions.

9.2.4.8 Dose and Administration

See Section 5.4.1 for additional administration guidelines. Dosing will be per package insert and investigator discretion.

9.2.4.9 Supplier

Relugolix is available commercially.

9.3 Stereotactic Body Radiation Therapy

9.3.1 Description

Stereotactic body radiation therapy will be performed on the True Beam Stx Machine utilizing 6MV photons using Rapid Arc (Varian, CA, USA).

9.3.2 Dosing and Administration

Patients will be immobilized in a custom cushion and CT will be performed in treatment planning position. Respiratory management will be taken into account utilizing 4DCT.

With radiology and consensus at multidisciplinary GU tumor board we will delineate the area of gross bone metastases and lymph node metastases and lung metastases. Contouring of metastases and organs at risk (OAR) in proximity to the metastatic tumor will be performed. The contouring of the metastases is the gross tumor volume (GTV). For SBRT there is no expansion of GTV to clinical target volume (CTV) to limit dose to normal tissue structures. For daily radiation setup error a 3-5mm margin with be applied to the GTV based on proximity to critical structures.

. We will plan the radiation therapy according to guidelines per NRG BR001, prior published RTOG studies and AAPM task force 101 guidelines as well as the recently published STOMP trial which also references AAPM task force 101 guidelines [14, 42].

Local control of gross oligometastatic sites will be determined by subsequent standard of care reimaging studies including CT chest/abdomen/pelvis and bone scan.

See Section 5.4.2for additional administration guidelines.

9.3.2.1 Human Toxicity

See Section 7.3 for details.

10.0 CORRELATIVE/ SPECIAL STUDIES

10.1 Tumor Tissue Clinical Testing

An overview of collection, processing, and analysis details are shown in Table 10.1.

The collection, processing and testing will be considered as part of routine care.

Table 10.1 Tumor tissue overview

Tissue Type	Primary (P) or Metastatic (M)?		Timepoint of collection	Receiving Laboratory	Clinical Laboratory Performing Analysis	Type of Downstream Research Analysis
	P	M				
• If available, archived formalin fixed paraffin embedded (FFPE) tissue	X	X	Baseline	COH Pathology	Foundation Medicine Inc.	• Via the Foundation One assay platform • Genomic alterations prior to development of castration resistance.
• *Optional* FFPE tissue from post-consent biopsy		X				

- *Baseline tissue*:
  - *FFPE*: If available, archived primary or metastatic specimen should be submitted following enrollment for clinical testing.
  - *Optional FFPE tissue from post-consent biopsy*: If participant is willing and feasible, attempts should be made to take extra metastatic tissue for clinical testing at time of standard of care biopsy.

10.1.1 Distribution to Foundation Medicine Inc.

The COH Pathology core will distribute de-identified tissue to Foundation Medicine Inc.(see Table 10.1). Downstream genomic analysis will be considered research. **NOTE:** Participant agreement is required in order for this research analysis to be performed (see consent document).

10.2 Correlative Blood Studies

Blood samples will be collected from an indwelling venous catheter or by venipuncture for the below stated analyses (see Table 10.2).

Table 10.2 Peripheral blood studies overview

Timepoint of collection	Volume per Timepoint	Tube Type	Processing / Receiving Laboratory	Laboratory Performing the Analysis	Type of Laboratory Analysis
• Cycle 1 Day 1 (Baseline) • Pre-Cycle 2 (Post-SBRT) • End of Ra223/EOT	20 mL	Sodium Heparin green top	Personnel in Dr. Marcin Kortylewski's laboratory	Dr. Marcin Kortylewski	Plasma and peripheral blood mononuclear cells (PBMC) isolation to assess immune factors and immune cells

10.2.1 Notification of Pending Collection, Blood Collection and Labeling

Notification of Pending Collection to Kortylewski Laboratory	Labeling and Collection Details	Post-collection Instructions
• Notify **at least one** day in advance) • **Send calendar invite via e-mail**: Seok White(sewhite@coh.org) or designee and cc: Dr. Marcin Kortylewski (MKortylewski@coh.org)	1. Label tubes with COH protocol #, subject ID, time of collection in 24-hour format, and timepoint of collection (e.g. D1C1 for Day1 of Cycle 1). 2. Timepoints of collection are stated in Table 10.2. 3. Invert tubes eight times after collection. 4. Place the tubes **on ice**.	• **Promptly** deliver the blood samples on ice to the Kortylewski Laboratory **within 1-2 hours (± 30 minutes).**

10.2.2 Processing of samples by Kortylewski laboratory

Samples will be processed per Kortylewski laboratory protocols for PBMC and plasma.

11.0 STUDY CALENDAR

All procedures may increase in frequency if clinically indicated.

Table11.0 Study Activity Calendar

Protocol Activities*	Screening [a]	Protocol Therapy [c, d]				Follow-up (Max. 5 years)	
		Cycle 1	Cycle 2	Cycle 3-7	Post Ra-223/EOT [i]	Response [j]	Long-term [k]
		Day 1 [e,f]	Day 1 [g,h]	Day 1 [g]			
Informed Consent [l]	X						
Medical History [m]	X						
Eligibility [n]	X						
Registration [o]	X						
Physical Exam [p] and Vital Signs [q]	X	X	X	X	X	X	
Height	X						
ECOG (Appx. A)	X	X	X	X	X	X	
Con-medications [r]	X	X	X	X	X	X	
AE assessment [s]		X [t]	X [t]	X [t]	X [t]	X [u]	X [u]
12-lead EKG	X [v]						
CBC with differential	X	X	X	X	X	X	
Serum chemistry [w]	X	X	X	X	X	X	
Prostate-specific antigen (PSA)	X [b]	X	X	X	X	X	
Serum testosterone	X [b]	X	X	X	X	X	
Immune-biomarker studies [x]		X	X		X		
Archival tumor tissue [y]	X						
Fresh tumor tissue [z]	X						
Tumor Evaluation [aa]	X				X	X [bb]	
ADT: Leuprolide **OR** goserelin**OR** degarelix OR relugolix [dd]	Dosing per package insert/ physician discretion for 36 weeks starting at least 28 days prior to SBRT						
Criteria to initiate stereotactic body radiation therapy (SBRT)		X [f]					
SBRT [f, cc]		X					
Criteria to initiate radium Ra 223 dichloride			X [h]				
Radium Ra 223 dichloride [h, cc]			Day 1 of each cycle				
Survival [k]							X

* Participants will receive bisphosphonate or RANKL inhibitor bone health agents at the dose and schedule consistent with the treatment of bone metastases or prevention of osteoporosis, starting approximately when protocol therapy begins until the participant's testosterone reaches normal levels (>50 ng/dL) or at the discretion of the PI.

a. Screening activities to occur within 56days prior to Cycle 1 Day 1 of protocol therapy **except** PSA and serum testosterone.

b. Screening PSA and serum testosterone should occur prior to 1st dose of androgen deprivation therapy (ADT). If not drawn prior to starting ADT, this will not constitute a protocol deviation as some patients will have started ADT prior to consenting on the trial
c. Protocol therapy may last until completion of 7 cycles of therapy, unacceptable toxicity or disease progression, whichever occurs first (see Section 5.7 for more comprehensive list).
d. In the absence of toxicity, each cycle lasts 28 ± 7 days.
e. *Cycle 1 Day 1*: With the exception of PSA, serum testosterone and blood counts other screening evaluations performed within 14 days prior to Cycle 1 Day 1 of protocol therapy may serve as Day 1 baseline evaluations.
f. Participants must meet criteria in Section 6.1 to initiate SBRT on Cycle 1 Day 1.
g. Assessments must be performed **within 7 days** prior to radium Ra 223 dichloride. Safety assessments must be reviewed within 7 days prior to initiating a new cycle.
h. *Cycle 2 Day 1 (1st dose of radium Ra 223 dichloride)*: Participants must meet criteria in Section 6.2.
i. *Post Ra-223/EOT visit to occur* approx. *28 days +/- 7 days post-last dose of Ra 223 dichloride*.
j. *Response follow-up* assessments for participants yet to progress, will occur ~ every 3 months (± 4 wks) (except tumor evaluations) from the day of last response evaluation until progression or the initiation of a new therapy.
k. *Long-term follow-up* assessments for participants who progressed or ended Response Follow-up to occur annually (± 30 days) or as requested by the Study PI via medical record review, review of social security registry/ public records, and/or telephone call.
l. *Informed consent* process to be fully documented (see Section 17.4). Informed consent must occur prior to any research only (non-SOC) screening procedures.
m. *Medical history* to include a review of treatment history, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
n. *Eligibility criteria* are detailed in Section 3.0.
o. *Registration* into a COH clinical trial management system (CTMS).
p. *Standard physical exam* includes weight and skin analysis.
q. *Vital signs*: heart rate, blood pressure, respiration rate, and temperature.
r. *Concurrent medications* and reason for administration to be documented in the EHR and eCRF from within 56 days prior to protocol therapy up to EOT visit. See Section 5.11.1for concomitant medication restrictions and guidelines.
s. *Adverse event (AE)* will be assessed using CTCAE v.5.0.
t. Active AE reporting will start from start of treatment until the post RA-223 visit/EOT visit **NOTE**: The highest AE grade per cycle will be reported in the eCRF from start of therapy until the EOT visit. **Exceptions to expedited reporting** are stated in Section 8.2
u. Long-term toxicities -- secondary malignancy, thyroid dysfunction-- attributed to protocol therapy will be collected via medical record review and/or phone call during Response Follow-up, standard of care visits and Long-term Follow-up. **NOTE:** If the participant is no longer at COH, the study team will request relevant medical information from the external institution.
v. If clinically indicated by history of cardiovascular disease.
w. *Serum chemistry* panel to include: glucose, Blood Urea Nitrogen (BUN), creatinine, total protein, albumin, magnesium, bicarbonate, calcium, sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT and AST.
x. *Immune biomarker studies*: Collect 20 mL per timepoint in sodium heparin green-top tubes and store on ice until delivery to Dr. Kortylewski's laboratory (See Section 10.2 for details). **NOTE:** Notification to the Kortylewski's laboratory of pending sample collection must be made **at least 1 day in advance** (see Section 10.2.1 for details).
y. *Tumor tissue: If available,* archival metastatic or primary tissue will be submitted for clinical testing. Refer to Section 10.1for additional details.

z. *Fresh metastatic tissue (optional)*: If the participant is willing attempts should be made to take extra metastatic tissue for clinical testing at the time of standard of care biopsy. See also Section 10.1.

aa. *Tumor Evaluation*: Options include combination of: CT chest, abdomen, pelvis, CXR, targeted X-rays, bone scan, Whole Body MRI, MRI of the TLS spine, MRI of the pelvis, PET/CT. All anatomical areas of the body need to be included (chest, abdomen, pelvis, skeleton) using combination of these tests. Follow up scans should at the minimum include the same scans utilized for screening.

bb. Tumor evaluation to occur every 6 months (± 14 days) from last tumor evaluation, and at PSA progression (unless taken within the last 4 weeks).

cc. Refer to Section 5.3 for the treatment plan. Refer to Section 6.3 for dose modification/ delay guidelines and Section 5.9 for supportive care guidelines.

12.0 ENDPOINT EVALUATION CRITERIA/MEASUREMENT OF EFFECT

12.1 Efficacy Endpoints

Response and progression will be evaluated in this study using modified Prostate Cancer Working Group 2 criteria [43] (see Appendix C and Appendix D). PSA levels will be a part of overall response assessment. Other clinical efficacy endpoints are described in Table 12.1.

Table 12.1 Efficacy Endpoints

Endpoint	Definition
Time to treatment failure (TTF)	Time from the initiation of ADT for metastatic disease until PSA increase to > pre-ADT level or PSA >10 (whichever is smaller) or radiographic or clinical progression or resumption of ADT by physician's choice
Objective response rate (ORR)	Proportion of patients achieving CR or PR at Cycle 8 Day 1 (post-6 doses of radium Ra 223 dichloride)
Complete response (CR) rate	Proportion of patients achieving CR
Progression-free survival (PFS)	Time from the initiation of ADT for metastatic disease until PSA progression or radiographic progression or death
Bone specific progression-free survival (Bs-PFS)	Time to progression of bone specific disease over baseline
Duration of response (DOR)	Time from documented response to recurrent or progressive disease is first met
Duration of overall complete response	Time from documented CR to recurrent/ progressive disease
Duration of stable disease	Time from start of treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.
Overall Survival (OS)	Date of initiation of protocol treatment to date of death from any cause

12.2 Toxicity

Toxicity will be graded according to the NCI CTCAE version 5.0.The highest AE grade per cycle will be reported in the eCRF from start of therapy until the end of treatment visit.

12.3 Alkaline phosphatase

Levels of alkaline phosphatase will be assessed at baseline and at the end of protocol therapy. The rate of normalization of the total alkaline phosphatase level (defined as a return to a value within the normal range) at the end of protocol therapy in patients with total alkaline phosphatase values above the upper limit of the normal range at baseline will be assessed.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This multimodality Phase2study is designed to test the preliminary efficacy and to determine if androgen deprivation therapy (ADT), stereotactic body radiation therapy (SBRT) and radium Ra 223 dichloride, all delivered at the standard doses are well-tolerated in patients with oligometastatic hormone sensitive prostate cancer. The motivation behind using the standard doses for each as the starting dose is due to the limited sites of SBRT permitted in this study (≤4 metastatic lesion) and the prior data of radium Ra 223 dichloride when combined with ADT in a more advanced disease setting which suggest that the standard dosing should be safe and appropriate[21].

Correlative tissue studies are also incorporated into this protocol to explore the prevalence of genomic alterations in this population. Additionally, changes in immune biomarkers over the course of ADT-radiotherapy will be analyzed in an exploratory manner.

13.2 Evaluable Participants

- ***Evaluable for toxicity***
  - Patients who received at least 1 SBRT dose will be evaluable for toxicity.
  - Patients who have received at least 1 dose of SBRT and at least 1 dose of Radium 223 will be evaluable for assessment of toxicity and efficacy.
- ***Evaluable for response***
  - Only those patients who have evaluable disease present at baseline, have received at least one dose of SBRT and at least 1 dose of radium Ra 223 dichloride, will be considered evaluable for response.

13.3 Accrual and Expected Duration of Trial

The sample size is 24 evaluable patients (as of July 2023 we had 1 inevaluable patient, therefore we will need to accrue a total of 25 patients to get 24 evaluable patients). Accrual is expected to be completed in 66 months.

Participant duration is planned for 68 months which includes protocol therapy (~ 8 months) and follow-up (5 years).

The estimated total study duration will be 134 months (~ 11 years), with 66 months of accrual and approximately 68 months of protocol therapy and follow-up for the last patient.

13.4 Stopping Rules for Excessive Toxicity

The stopping rules for safety/toxicity will be assessed for each patient after the first 2 cycles of radium dichloride 223. The expected rate of unacceptable toxicity should not be ≥33%.

A patient will be deemed to have experienced an Unacceptable Toxicity (UT) if any of the following occur during the **first 2 cycles of radium Ra 223 dichloride (Cycles 2 and 3)** and are attributed as possibly, probably, or definitely related to protocol therapy:

- *Hematological*
  - Any ≥ Grade 3 hematological toxicity that delays the next planned dose of radium Ra 223 dichloride by > 28 days

- *Non-hematological*
  - Any >Grade 2 fracture
  - Any ≥ Grade 3 non-hematological toxicity that does not resolve to ≤ Grade 2 with adequate supportive care and delays the next planned dose of radium Ra 223 dichloride by> 28 days
  - Any recurrent ≥ Grade 3 toxicity

The following table will be consulted as relevant toxicities defined above are encountered.

When a stopping rule is triggered, the study PMT will review and assess the safety of the trial and submit a report to the COH DSMC. The COH DSMC will review for approval any decision to continue accrual, amendment the protocol, or permanently suspend accrual to the trial.

# of patients treatedthat determines early stopping	# of patients with unacceptable toxicity	Given the following toxicity rates, cumulative probability of early stopping:		
		10%	25%	35%
<=6	2	0.11	0.47	0.68
<=10	3	0.14	0.56	0.80
<=12	4	0.14	0.58	0.81
<=15	5	0.14	0.59	0.83
<=18	6	0.14	0.60	0.85
<=21	7	0.14	0.61	0.86
<24	8	0.14	0.61	0.86

13.5 Statistical Analysis Plan

With 24 evaluable patients treated we will estimate median time to treatment failure (radiographic or PSA progression, death or cessation of treatment due to clinical progression or toxicity). Our historical data suggest a 16 month median time to TTF [10]. Other studies varied in results and endpoints used, ranging from a median time to failure of 11 months [45], median distant progression free survival of 21 months [46], and median time to clinical progression of 18 months[23]. Even when permitting a lower PSA entry criteria (PSA>0.2) the median time to progression was 21 months[14]. (Note: This observation has allowed us to amend this study to permit that lower PSA entry criteria to help with accrual). We seek to demonstrate a median TTF of at least 25 months, exceeding reports from all previous prior studies that examined only a two modality approach. With 24 evaluable patients, accrued over 16 months and followed for 18 months, we will have greater than 80% power to detect an improvement in TTF from 16 months to 32 months with a one-sided type I error of 10%. The critical value for a promising median TTF based on this design is 25 months, or an improvement of 9 months over our historical data. If patients experience treatment failure at ONLY an untreated asymptomatic low volume locoregional recurrence (allowed per amendment 6 based on PI discretion), TTF will be censored at that time for that patient.

Other secondary analysis will include progression-free survival, overall survival, complete response rate, duration of response, and duration of overall complete response, bone specific progression-free survival and duration of stable disease.

Exploratory analysis will include describing the rate of normalization of the total alkaline phosphatase level at the end of protocol therapy and evaluation of the role of genomic mutations and immune biomarker

studies on outcome and toxicity. These outcomes will be reported to provide further support, combined with the activity, and tolerability to help guide additional studies.

14.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

14.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

14.2 Data Capture Methods and Management

Data for this trial will be collected using City of Hope's electronic capture system that is compliant with 21 CFR Part 11.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

14.3 Case Report Forms/Data Submission Schedule

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

The investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated in Section 14.2, and will be submitted according to the timelines indicated in Table 14.3.

Table 14.3 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 10 calendar days of treatment administration
Adverse Event Report Forms	Within 7 calendar days of AE assessment/notification
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms (concomitant medications)	Within 10 calendar days of the assessment
Off Treatment/Off Study Forms	Within 10 calendar days of end of treatment/study
Follow up/Survival Forms	Within 14 calendar days of the follow up activity

14.4 Regulatory Records

The investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

15.0 ADHERENCE TO THE PROTOCOL

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. Protocol deviations may be on the part of the subject, the investigator, or study staff.

All deviations from the protocol must be documented in study subject source documents and promptly reported. The Study PI will report the deviation according to City of Hope's deviation policy for reporting deviations (See Section 8.0).

16.0 STUDY OVERSIGHT, QUALITY ASSURANCE, AND DATA & SAFETY MONITORING

16.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

All investigators agree to:

- Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when necessary to protect the safety, rights or welfare of subjects.
- Personally conduct or supervise the study (or investigation).
- Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
- Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
- Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
- Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
- Seek IRB and Sponsor approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

16.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities as defined in § 21 CFR 312.

16.3 Protocol Management Team (PMT)

Refer to Section 8.0.

16.4 Auditing

Clinical site auditing is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Auditing for this study will be performed by the City of Hope Office of Clinical Trials Auditing and Monitoring (OCTAM).

Documentation of audit activities and findings by OCTAM will be provided to the study team, the PI, and the COH DSMC.

16.5 City of Hope Data and Safety Monitoring Committee

The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials that are sponsored by City of Hope. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. The committee reviews the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. Information that raises any questions about participant safety will be addressed with the Principal Investigator, statistician and study team. Refer to Section 8.0 for details.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

17.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved **protocol** and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- State of California Health and Safety Code, Title 17
- Institutional policies and procedures

17.3 Institutional Review Board

In accordance with City of Hope policies, an Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent document will be in the possession of the investigator before the study is initiated.

The IRB will be informed of revisions to other documents originally submitted for review; serious unexpected or unanticipated adverse experiences occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

Any amendment to the protocol document and accompanying informed consent document/template, as developed and provided by the PI, will require review and approval by the COH IRB before the changes are implemented in the study.

17.4 Informed Consent

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

Before implementing any study procedure, informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the prospective participant or his/her legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation

17.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures (safety visit) and chart review and survival follow-up.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

17.6 Special and Vulnerable Populations

17.6.1 Inclusion of Women and Minorities

Women are excluded from participation because prostate cancer is a disease of men. The study is open to any male regardless of ethnicity. If differences in outcome that correlate to racial or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

17.6.2 Exclusion of Pediatric Patients

Pediatric recipients (children <18 years old of age) are excluded from this study because prostate cancer is not present in this population.

17.6.3 HIV Positive Individuals

Patients with controlled HIV will be included because those with well-controlled disease should not be at increased risk of developing neutropenia compared to other patients.

17.6.4 Vulnerable Populations

45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, or economically or educationally disadvantaged persons as vulnerable populations.

Adults lacking capacity to consent are not excluded from participation. This study does not pose additional risks for adults lacking capacity than for the general population. In such instances, informed consent will be sought and documented from the prospective participant's legally authorized representative in agreement with institutional policies and local IRB approval.

17.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed participant authorization informing the participant of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, ant the rights of a research participant to revoke their authorization for use of their PHI. In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants 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 participant is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of participants will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

The investigator/institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring/auditing, IRB reviews, and FDA/regulatory authority inspections. The participant's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

17.8 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

17.9 Financial Obligations, Compensation, and Reimbursement of Participants

Radium Ra 223 dichloride will be provided free of charge to participants.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

The standard of care drug(s) and standard of care procedures provided will be the responsibility of the research participant and/or the insurance carrier. The research participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The research participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the research participant were not in a research study.

In the event of physical injury to a research participant, resulting from research procedures, appropriate medical treatment will be available at the City of Hope to the injured research participant, however, financial compensation will not be available.

The research participant will not be paid for taking part in this study.

17.10 Publication/Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement between City of Hope and Bayer. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov and results will be reported on ClinicalTrials.gov within 12 months of the estimated or actual completion date of the trial, whichever date is earlier.

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APPENDIX A: PERFORMANCE STATUS

ECOG Performance Scale[47]	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: STAGING CRITERIA

Stage	Sub-stage	Definition
Metastasis		Systemic spread
	M0	No distant metastasis
	M1a	Non-regional lymph node metastasis
	M1b	Bone metastasis 1) Axial skeleton only 2) Extending also to peripheral skeleton
	M1c	Metastasis at other sites

APPENDIX C: DISEASE PARAMETERS AND METHODS FOR EVALUATION

Response and progression will be evaluated in this study using modified Prostate Cancer Working Group 2 criteria [43].

Disease Parameters

- **Measurable disease:**

  Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >10mm with conventional techniques (CT, MRI, or caliper measurement) and as >20mm by chest X-ray (if clearly defined and surrounded by aerated lung.) Lymph nodes greater than 15mm on short axis are considered measureable as well. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

- **Non-measurable disease:**

  All other lesions (or sites of disease), including small lesions (longest diameter <20 mm by chest X-ray or <10 mm using CT, MRI or caliper measurement), are considered non-measurable disease. Organomegaly, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI are all non-measurable.

- **Target lesions:**

  All 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. Lymph nodes less than 15mm in the short axis cannot be used as target lesions. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

- **Non-target lesions:**

  All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Methods 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 and never more than 30 days before the beginning of the treatment.

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 antitumor 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). 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, CT is preferable.

- **Conventional CT and MRI:**

  These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols

- **Ultrasound (US):**

  When the primary endpoint of the study is objective response evaluation, US 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. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination

- **Endoscopy, Laparoscopy:**

  The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

- **Tumor markers:**

  Baseline PSA is defined as the last known PSA prior to the onset of ADT (anti-androgen or LHRH agonist/antagonist).PSA response criteria will be a part of overall response assessment and will also be recorded as a separate PSA response criteria. They are follows:

  - PSA CR - PSA <0.04 confirmed at least 3 weeks later
  - PSA PR - PSA decline by >50 % from baseline, confirmed at least 3 weeks later
  - PSA SD - PSA not meeting criteria for CR, PR or PD

- PSA PD - PSA increase by ≥ 25 % over baseline and to at least PSA >2 ng/mL confirmed at least 3 weeks later

- **Cytology, Histology:**

  These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

  The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

APPENDIX D: RESPONSE CRITERIA

Response and progression will be evaluated in this study using modified Prostate Cancer Working Group 2 criteria [43].

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Lymph node CR is when the lymph node has decreased to less than 10mm in the short axis.
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (including the baseline scan if that is the smallest), and at least a 5mm increase or the appearance of new lesions.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and PSA level <0.04 (undetectable)
Incomplete Response/Stable Disease (SD)	Persistence of one or more non-target lesion(s) and/or of PSA ≥0.04 but no increase ≥ 25 % over baseline and to at least PSA >2 ng/mL
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. . PSA increase by ≥ 25 % over baseline and to at least PSA >2 ng/mL . However, unequivocal progression should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of measurement criteria, but confirmation is not necessary.

Target Lesions	Non-Target Lesions	New Lesions	PSA	Overall Response
CR	CR	No	<0.04	CR
CR	Non-CR/Non-PD	No	Decline by >50% from baseline –pre ADT	PR
PR	Non-PD	No	Decline by >50% from baseline –pre ADT	PR
SD	Non-PD	No	No increase by 25 % over baseline and to a value of >2 ng/dL	SD

Target Lesions	Non-Target Lesions	New Lesions	PSA	Overall Response
PD	Any	Yes or No	Any	PD
Any	PD*	Yes or No	Any	PD
Any	Any	Yes	Any	PD
Any	Any	Any	increase by 25 % over baseline and to a value of >2 ng/dL	PD

*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.